Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Assess the Efficacy and Safety of Lu AA21004 in Patients with Major Depressive Disorder

NCT Number: NCT02389816

Protocol Approve Date: 18-Aug-2015

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

PROTOCOL

<Title>

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Evaluate the Efficacy and Safety of Once Daily Oral Lu AA21004 in Patients with Major Depressive Disorder

<Short Title>

A Phase III Study of Lu AA21004 in Patients with Major Depressive Disorder

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi		
Study Number:	Lu AA21004/CCT-004		
Edition:	Protocol Incorporating Amendment No. 2		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Lu AA21004		
Date:	18 August 2015		

Amendment History

Date	Amendment Number	Region
9 January 2015	Initial Protocol	All Study Sites
7 May 2015	Amendment 1	All Study Sites
18 August 2015	Amendment 2	All Study Sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

Refer to the attachment.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** Lu AA21004	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Evaluate the Efficacy and Safety of Once Daily Oral Lu AA21004 in Patients with Major Depressive Disorder	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: Lu AA21004/CCT-004	**Phase:** 3	

Study Design:

This is a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the efficacy and safety of 8-week treatment of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) in Japanese subjects with major depressive disorder (MDD).

This study consists of a 1- to 3-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week safety follow-up period. Subjects who fulfill all inclusion criteria and none of exclusion criteria at the start of screening period (Visit 1) and at the start of placebo lead-in period (Visit 2) will move into the placebo lead-in period and receive placebo once daily for 1 week in a single-blind manner. Afterwards, these who fulfill all the inclusion criteria and none of the exclusion criteria at the start of double-blind treatment period (Visit 3) will move into the double-blind treatment period and will be randomized in a 1:1:1 ratio to one of the following treatment groups: the placebo group, the Lu AA21004 10 mg/day group or the Lu AA21004 20 mg/day group. Subjects in the placebo group and the Lu AA21004 10 mg/day group will receive placebo and Lu AA21004 10 mg, respectively, once daily from the day after Visit 3 for 8 weeks in a double-blind manner. Subjects in the Lu AA21004 20 mg/day group will receive Lu AA21004 10 mg once daily from the day after Visit 3 for 1 week and thereafter Lu AA21004 20 mg once daily for 7 weeks in a double-blind manner. Subjects in any treatment groups will visit study sites at Week 1, 2, 4, 6 and 8 during the double-blind treatment period for examinations/observations/assessments.

A safety follow-up contact (visit or phone call) will be made 4 weeks after the completion of the double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or the double-blind treatment period will be requested to visit the study site for the end-of study assessments within 7 days after the discontinuation decision is made wherever possible, and will be contacted 4 weeks after the last dose of the study medication for safety follow-up.

Primary Objective:

- To evaluate the efficacy of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.

Secondary Objectives:

- To evaluate the safety and tolerability of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.
- To evaluate the efficacy of Lu AA21004 (10 or 20 mg/day) on cognitive functions after 8 weeks of treatment in Japanese patients with MDD.

Additional Objective:

- To analyze the plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 using population pharmacokinetic analyses.

Subject Population:

Male and female subjects, aged between 20 and 75 years (both inclusive), with recurrent MDD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria.

Number of Subjects: Randomized subjects: 480 (160 per group)	**Number of Sites:** Approximately 60 sites
Dose Levels: Placebo lead-in period: Placebo once daily Double-blind treatment period: Lu AA21004 (10 or 20 mg) or placebo once daily	**Route of Administration:** Oral
Duration of Treatment: 9 weeks in total Placebo lead-in period: 1 week Double-blind treatment period: 8 weeks	**Period of Evaluation:** 14 to 16 weeks in total Screening period: 1 to 3 weeks Placebo lead-in period: 1 week Double-blind treatment period: 8 weeks Safety follow-up period: 4 weeks

Main Criteria for Inclusion:

- The subject suffers from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x).
- The subject is a man or a woman aged 20 to 75 years (both inclusive) at the time of informed consent.
- The reported duration of the current major depressive episode is 3 to 12 months (both inclusive) at the start of screening period.
- The subject has a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26, a Hamilton Depression Rating Scale (HAM-D17) total score ≥18, and a clinical global impression scale-Severity (CGI-S) score ≥4 at the start of screening period, the start of placebo lead-in period and the start of the double-blind treatment period.

Main Criteria for Exclusion:

- The subject has any following current or past history of psychiatric disorder and/or neurological disorder:
  - Any current psychiatric disorder other than MDD as defined by DSM-IV-TR (To be assessed by Mini International Neuropsychiatric Interview: MINI). A subject who exhibits symptoms of anxiety is eligible unless the subject fulfills the diagnostic criteria for a current anxiety disorder per DSM-IV-TR.
  - Current diagnosis or history of manic, mixed or hypomanic episode, MDD with psychotic features, schizophrenia or any other psychotic disorder (including substance-related mental disorders, or mental disorders due to a general medical condition) as defined by DSM-IV-TR.
  - Current diagnosis or history of any substance-related disorder (except nicotine and caffeine-related disorders) as defined by DSM-IV-TR.
  - The subject with a positive urine drug screening result at the start of screening period or the start of placebo lead-in period. In case that a subject showed positive test result at the start of screening period because the test was conducted before washout of pretreatment drugs, the subject is eligible as long as he/she shows negative result at the start of placebo lead-in period.
  - Presence or history of any clinically significant neurological disorder (including epilepsy).
  - Any neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).
  - Any DSM-IV-TR axis II disorder.
- The subject has the current or previous major depressive episode which were considered by the investigator to have been resistant to 2 or more adequate antidepressants treatments of at least 6 weeks duration each at sufficient doses.

- The subject has received any augmentation therapy (e.g. lithium, T3/T4, lamotrigine, sodium valproate, carbamazepine, additional atypical antipsychotic, or concomitant use of other antidepressant, etc.) for the current major depressive episode.
- In the opinion of the investigator, the subject has experienced significant number of major depressive episodes in the past, and is suspected of disease other than MDD.
- In the opinion of the investigator, the subject has experienced the first major depressive episode at his/her young age, and is suspected of disease other than MDD.
- The subject has a MADRS total score at the start of double-blind treatment period that has improved or aggravated by 25% or more from the score at the start of placebo lead-in period.
- The subject is at significant risk of suicide or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS at the start of screening period, the start of placebo lead-in period or the start of double-blind treatment period, or has attempted suicide within 6 months prior to the start of screening period.
- The subject has experienced any environmental change (e.g. temporary retirement, returnment, change of residence) considered by the investigator to have the potential to impact on the efficacy evaluation, or plans such environmental changes during the study.
- The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, neoplastic, skin and subcutaneous tissue disorders, eye disorders, or metabolic disturbance.

Main Criteria for Evaluation and Analyses:

Efficacy Endpoints

Primary Endpoint

- Change from baseline (i.e. at the start of double-blind treatment) in the MADRS total score after 8 weeks of treatment

Secondary Endpoints

- MADRS response after 8 weeks of treatment (last observation carried forward [LOCF])
  (MADRS response is defined as a ≥50% decrease in the MADRS total score from baseline).
- MADRS remission after 8 weeks of treatment (LOCF)
  (MADRS remission is defined as the MADRS total score of ≤10).
- Change from baseline in the HAM-D17 total score after 8 weeks of treatment (LOCF).
- Clinical global impression scale-Improvement (CGI-I) score after 8 weeks of treatment (LOCF).
- Change from baseline in the CGI-S score after 8 weeks of treatment (LOCF).
- Change from baseline in the Sheehan Disability Scale (SDS) total score after 8 weeks of treatment (LOCF).
- Change from baseline in the Digit Symbol Substitution Test (DSST) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Perceived Deficits Questionnaire (PDQ-5) score after 8 weeks of treatment (LOCF).

Pharmacokinetic Endpoint

- Plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835.

Safety Endpoints

- Adverse events
- Weight
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Considerations:

Change from baseline (i.e. the start of double-blind treatment period) in the MADRS total score after 8 weeks of treatment is the primary efficacy endpoint. Comparisons between each Lu AA21004 treatment group and the placebo group at Week 8 of the double-blind treatment period will be performed using the full analysis set (FAS) based on Mixed Model for Repeated Measures (MMRM) analysis of covariance with the change from baseline in the MADRS total score as a dependent variable, and visit, treatment group, visit-by-treatment group interaction and baseline MADRS total score-by-time point interaction as fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom. Holm's step-down method will be used to adjust the multiplicity for the comparisons.

Sample Size Justification:

A number of subjects planned to be enrolled in this study is 480 (160 per group). Assuming the true mean differences of 3.5 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between each Lu AA21004 group and the placebo group by 2-sample t-test. In addition, assuming the true mean differences of 3.0 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between either the Lu AA21004 10 mg or 20 mg group and the placebo group. These power calculations assume a common standard deviation of 9.5 for the change from baseline in the MADRS total score, with a 2-sided level of 0.025.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ANCOVA	analysis of co-variance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
Cavg	average plasma concentration at steady state
CGI-I	clinical global impression scale-Improvement
CGI-S	clinical global impression scale-Severity
Cmax	maximum observed plasma concentration
COX	cyclooxygenase
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P-450
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSST	Digit Symbol Substitution Test
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transferase
HAM-D	Hamilton Depression Rating Scale
hCG	Human chorionic gonadotropin
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation
INR	international normalized ratio
LDL	low-density lipoprotein
LOCF	Last Observation Carried Forward
MADRS	Montgomery Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model for Repeated Measures
NaSSA	noradrenergic and specific serotonergic antidepressant
NSAIDs	non-steroidal anti-inflammatory drug
PDQ	Perceived Deficits Questionnaire
PMDA	Pharmaceutical and Medical Devices Agency

PT	Preferred Term
PTE	Pretreatment Event
PTP	press through package
QIDS	Quick Inventory of Depressive Symptomatology
SAE	serious adverse event
SDS	Sheehan Disability Scale
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	selective serotonin reuptake inhibitor
SUSARs	Suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TSH	thyroid-stimulating hormone
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Lu AA21004 (generic name: vortioxetine hydrobromide) is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and 5-HT transporter (5-HTT) inhibitor. This novel antidepressant with a different profile from existing medications has been under development in Japan and overseas. As of December 2014, Lu AA21004 has been approved for marketing as a drug for the treatment of MDD in countries including the U.S., Europe and Australia.

Depression is a mental disease mainly characterized by a depressed mood and a loss of interest or pleasure, and is additionally characterized by thought or concentration difficulties, an appetite decrease or increase, anxiety, a feeling of worthlessness or guilt, and thoughts related to suicide (suicidal ideation) as well as somatic symptoms including sleep disturbances and fatigability.[1][2] With advances of basic research and clinical studies, the etiology and pathology of depression have been gradually revealed, but not fully elucidated so far.

Depression is a common disease worldwide, with the estimated lifetime prevalence above 10%. The onset age is estimated to be from 20 to 50 years old in half of patients; however, the onset in children and the elderly has been also reported.[3] In the U.S., the prevalence of depression in aged 18 to 29 years is approximately 3-fold higher than that in more than 60 years, and, after early adolescence, the prevalence in women is 1.5 to 3-fold higher than in men, showing that the prevalence of depression varies widely depending on age and sex.[4]

The course of depression varies from only 1 episode in a lifetime to a lifelong disorder with recurrent episodes, and some patients suffer from long-term depressive symptoms despite treatments. Depression is therefore a significant mental and social burden and economic loss for not only patients but also their family, which treatment is necessary.[3]

The goal of treatment for depression is to improve patients' mental and social quality of life by effectively alleviating the depressive symptoms. Depression is mainly treated with pharmacotherapy and psychotherapy, and these treatments are selected according to the severity and pathological condition.[3] As pharmacotherapy in patients with moderate to severe depression, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) have been widely used. These antidepressants, however, have problems such as patients with inadequate response and adverse effects; therefore, development of an antidepressant with a novel profile can broaden treatment options and optimize treatment for depression.

4.1.1 Clinical Pharmacology

Results of clinical pharmacology studies in Japan and overseas are summarized below.

Lu AA21004 was slowly absorbed after oral administration, and the Tmax was approximately 7 to 11 hours. The absolute bioavailability of Lu AA21004 was approximately 75%. The

pharmacokinetics of Lu AA21004 was linear within the dose range between 2.5 and 60 mg. The plasma concentration of Lu AA21004 reached steady state after approximately 2-week multiple doses, and the accumulation index was 5 to 6 based on AUC following multiple doses of 5 to 20 mg/day. There was no food effect on the pharmacokinetics of Lu AA21004.

Lu AA21004 was extensively metabolized in the liver, primarily through oxidation or glucuronic acid conjugation, and CYP2D6 was shown to be the primary enzyme in metabolism of Lu AA21004 to the major metabolite Lu AA34443. Lu AA34443 was pharmacologically inactive, and the active metabolite Lu AA39835 did not cross the blood-brain barrier, although Lu AA39835 was slightly detected in plasma, suggesting that these metabolites are less likely to contribute to the pharmacological effect of Lu AA21004. In addition, Lu AA21004 and its metabolites did not induce or inhibit CYP isozymes *in vitro*, suggesting that clinical significant drug-drug interactions with Lu AA21004 are less likely to occur.

The T1/2 of Lu AA21004 was approximately 66 hours, and two- thirds of its metabolites were excreted in urine, and one-third were excreted in feces. The excretion of unchanged Lu AA21004 was slightly noted in feces.

After multiple doses of Lu AA21004, 5-HTT occupancy in raphe nuclei was approximately 50% at doses of 5 mg/day, 65% at 10 mg/day, and 80% or more at 20 mg/day.

Based on results of studies in Caucasian and Japanese subjects, there were no statistically significant differences in the pharmacokinetics and 5-HTT occupancy of Lu AA21004 between the races.

4.1.2 Overseas Phase II/III Clinical Studies

A total of 12 overseas placebo-controlled, double-blind, short-term studies (Studies 11492A, 11984A, 303, 304, 305, 13267A, 315, 316, 317, CCT-002, 12541A and 14122A) were conducted to evaluate the efficacy of Lu AA21004 for the treatment of MDD. Study CCT-002 was a multinational study including Japan.

The changes from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score were analyzed by mixed model repeated measures (MMRM) in the individual studies; and the results of the 11 of 12 studies mentioned above except for Study 12541A for elderly patients were used for meta-analysis. As for the mean changes from baseline in the MADRS total score at Week 6 or 8, the differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were -2.3 ($p = 0.007$), -3.6 ($p < 0.001$) and -4.6 ($p < 0.001$), respectively, and all of them were statistically significant. In addition, although the mean difference between the 15 mg group and placebo group was -2.6, not statistically significant. MADRS response rate (MADRS response is defined as a $\geq 50\%$ decrease from baseline in the MADRS total score) in the subjects treated with Lu AA21004 was 46% to 49%, whereas that in the subjects treated with placebo was 34% ($p < 0.01$). These results suggested Lu AA21004 at doses of 5 to 20 mg/day was effective.

For comprehensive safety evaluation including the above-mentioned short-term studies and long-term studies (Studies 11492C, 11984B, 301, 13267B and 314), treatment with Lu AA21004 at doses of 5 to 20 mg/day was safe and well tolerated. The most common TEAE in the

Lu AA21004 groups was nausea, and gastrointestinal TEAEs were occurred more frequently in female than male. Most TEAEs were mild or moderate and occurred within the first 2 weeks of treatment. In addition, TEAEs were usually transient, and did not generally lead to discontinuation of the study medication.

Abrupt discontinuation of antidepressants may result in discontinuation symptoms, however, there were no clinically relevant differences in the incidence or nature of discontinuation symptoms between the Lu AA21004 groups and placebo group.

The incidence of self-report sexual dysfunction in the Lu AA21004 groups was low, and was similar to that in the placebo group. In the study using a rating scale (Arizona Sexual Experience Scale) for sexual dysfunction, the incidence of sexual dysfunction at doses of 5 to 15 mg/day of Lu AA21004 was similar to that of placebo, but that at 20 mg/day was higher than placebo.

Lu AA21004 had no clinically significant effect on weight, heart rate, blood pressure, and hepatic and renal functions. Moreover, Lu AA21004 also had no clinically significant effect on ECG parameters (QT interval, QTc interval, PR interval and QRS interval). In a thorough QTc study in healthy adult subjects, Lu AA21004 at doses up to 40 mg/day had no potential for prolongation of QT/QTc intervals.

4.1.3 Japanese Phase II/III Clinical Studies

In Japan, 2 placebo-controlled, short-term studies (Study CCT-002 [multinational study] and Study CCT-003 [Japan local study]) were conducted in subjects with MDD. In addition, a long-term extension study (Study OCT-001) was conducted in those who completed Study CCT-003.

Study CCT-002 was conducted in 14 countries including Japan, Europe and the Asia Pacific region to evaluate the efficacy and safety of Lu AA21004 at doses of 5, 10 and 20 mg/day. For the mean changes from baseline in the MADRS total score at Week 8 (last observation carried forward [LOCF]) in the primary efficacy analysis (analysis of covariance [ANCOVA]), the mean differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were -0.61 ($p = 0.91$), -1.69 ($p = 0.30$) and -1.82 ($p = 0.24$), respectively. In addition, in the same analysis for Japanese population, the mean differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were 0.89, -2.74 and -3.45, respectively.

In Study CCT-002, Most TEAEs were mild or moderate, and TEAEs reported in more than 5% of subjects in any Lu AA21004 groups were nausea, nasopharyngitis, headache, dizziness, constipation, dry mouth, and insomnia. Of these, TEAEs with higher ($\geq$ 2-fold) incidence in any Lu AA21004 groups than that in placebo group were nausea, constipation, dry mouth, dizziness and insomnia.

In Study CCT-003, the efficacy and safety of Lu AA21004 at doses of 5 and 10 mg/day were evaluated in Japanese subjects with MDD. For the mean changes from baseline in the MADRS total score at Week 8 (LOCF) in the primary efficacy analysis (ANCOVA), the mean differences of the Lu AA21004 5 and 10 mg group compared to the placebo group were -2.03 ($p = 0.10$) and -1.04 ($p = 0.40$), respectively.

In Study CCT-003, TEAEs reported in more than 5% of subjects in any Lu AA21004 groups were nausea, diarrhoea, nasopharyngitis, somnolence, headache, and suicidal ideation. Of these, TEAEs with higher (≥2-fold) incidence in the Lu AA21004 groups than that in the placebo group were nausea and suicidal ideation. For suicidal ideation, the incidence in the 10 mg group (8 subjects; 6.6%) was higher than in the placebo group (2 subjects; 1.6%) and 5 mg group (1 subject; 0.8%). In general, most TEAEs were mild or moderate, suggesting that there were no significant safety concerns about Lu AA21004.

In the open-label long-term extension study (Study OCT-001), the safety of 52 week treatment of Lu AA21004 at flexible doses of 5 to 20 mg/day was evaluated in subjects who completed Study CCT-003. In Study OCT-001, TEAEs reported in more than 5% of subjects were nasopharyngitis, nausea, seasonal allergy, headache, weight increased, diarrhoea, vomiting, alanine aminotransferase (ALT) increased, somnolence, malaise, influenza, and blood creatine phosphokinase increased. No long-term specific TEAEs were observed, and most TEAEs were mild or moderate, suggesting that there were no significant safety concerns in a long-term treatment of Lu AA21004.

4.2 Rationale for the Proposed Study

In Europe and the U.S., the efficacy and safety of Lu AA21004 were demonstrated at doses of 5 to 20 mg/day and Lu AA21004 has already been approved for marketing. For 2 short-term studies (Studies CCT-002 and CCT-003) including Japanese MDD patients, there are no statistically significant differences in the efficacy between any Lu AA21004 groups and the placebo group; however, in Study CCT-002, changes from baseline in the MADRS total score in the 10 and 20 mg groups were grater than in the placebo group in both overall population and Japanese population, and these results appeared to be supported by the result of 10 mg group in Study CCT-003.

Based on these results, if a statistically significant difference between the Lu AA21004 10 or 20 mg group and the placebo group is shown in the planned study (Study CCT-004), it is considered that the hypothesis of the efficacy of Lu AA21004 at doses of 10 and 20 mg in the Japanese population in Study CCT-002 can be verified.

The results of Studies CCT-002, CCT-003 and OCT-001 suggested that there were no significant safety concerns about Lu AA21004 at the dose up to 20 mg, but further data collection may provide more appropriate safety evaluation.

From the above, this study is designed as an additional phase III study to evaluate the efficacy and safety of Lu AA21004 in Japanese patients with MDD.

Pharmacogenomic analyses may be conducted to evaluate a possible contribution of genetic polymorphism on drug response affecting the efficacy and safety of Lu AA21004. Participation of subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research with banked samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the efficacy of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.

5.1.2 Secondary Objectives

- To evaluate the safety and tolerability of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.
- To evaluate the efficacy of Lu AA21004 (10 or 20 mg/day) on cognitive functions after 8 weeks of treatment in Japanese patients with MDD.

5.1.3 Additional Objectives

- To analyze the plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 using population pharmacokinetic analyses.

5.2 Endpoints

5.2.1 Efficacy Endpoints

5.2.1.1 Primary Endpoint

- Change from baseline (i.e. at the start of the double-blind treatment period) in the MADRS total score after 8 weeks of treatment.

5.2.1.2 Secondary Endpoints

- MADRS response after 8 weeks of treatment (LOCF).
  (MADRS response is defined as a ≥50% decrease in the MADRS total score from baseline).
- MADRS remission after 8 weeks of treatment (LOCF).
  (MADRS remission is defined as the MADRS total score of ≤10).
- Change from baseline in the Hamilton Depression Rating Scale (HAM-D17) total score after 8 weeks of treatment (LOCF).
- Clinical global impression scale-Improvement (CGI-I) score after 8 weeks of treatment (LOCF).
- Change from baseline in the clinical global impression scale-Severity (CGI-S) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Sheehan Disability Scale (SDS) score after 8 weeks of treatment (LOCF).

- Change from baseline in the Digit Symbol Substitution Test (DSST) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Perceived Deficits Questionnaire (PDQ-5) score after 8 weeks of treatment (LOCF).

5.2.2 Pharmacokinetic Endpoint

- Plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835.

5.2.3 Safety Endpoints

- Adverse events
- Weight
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

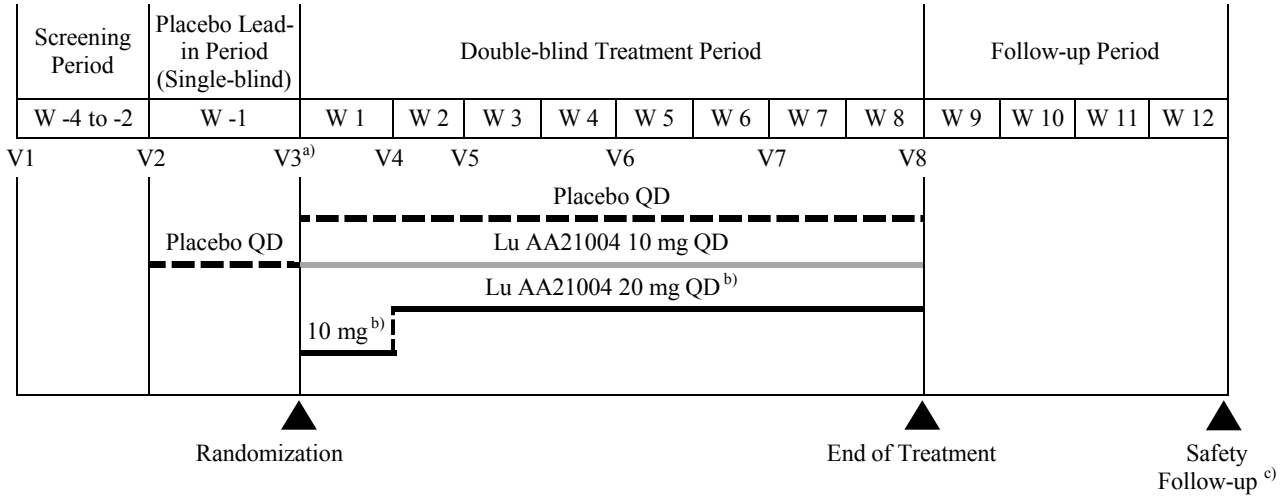
This is a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the efficacy and safety of 8-week treatment of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) in Japanese subjects with MDD.

This study consists of a 1-to 3-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week safety follow-up period. Subjects who fulfill all inclusion criteria and none of exclusion criteria at the start of screening period (Visit 1) and at the start of placebo lead-in period (Visit 2) will move into the placebo lead-in period and receive placebo once daily for 1 week in a single-blind manner. Afterwards, these who fulfill all the inclusion criteria and none of the exclusion criteria at the start of double-blind treatment period (Visit 3) will move into the double-blind treatment period and will be randomized in a 1:1:1 ratio to one of the following treatment groups: the placebo group, the Lu AA21004 10 mg/day group or the Lu AA21004 20 mg/day group. Subjects in the placebo group and the Lu AA21004 10 mg/day group will receive placebo and Lu AA21004 10 mg, respectively, once daily from the day after Visit 3 for 8 weeks in a double-blind manner. Subjects in the Lu AA21004 20 mg/day group will receive Lu AA21004 10 mg once daily from the day after Visit 3 for 1 week and thereafter Lu AA21004 20 mg once daily for 7 weeks in a double-blind manner. Subjects in any treatment groups will visit study sites at Week 1, 2, 4, 6 and 8 during the double-blind treatment period for examinations/observations/assessments.

A safety follow-up contact (visit or phone call) will be made 4 weeks after the completion of the double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or the double-blind treatment period will be requested to visit the study site for the end-of study assessments within 7 days after the discontinuation decision is made wherever possible, and will be contacted 4 weeks after the last dose of the study medication for safety follow-up.

A schematic of the study design is shown in Figure 6.a.

A schedule of examinations/observations/assessments is listed in Appendix A.



W: week, V: visit, QD: once daily
a) Subjects will be randomized on the day of visit at the start of double-blind treatment period (Day -1). Subjects will start the double-blind treatment from the next day (Day 1).
b) Subjects will receive 10 mg/day for the first 1 week, and then increase the dose to 20 mg/day from the 2nd week.
c) Safety follow-up assessment will be conducted by visit to the site or on telephone.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Subject Population

It has been reported that the placebo response rate in subjects with single major depressive episode is higher than that in subjects with recurrent major depressive episode.[5] Since it is important to exclude subjects with high placebo response from clinical studies of antidepressants, subjects with recurrent major depressive episode are eligible for this study. In order to adequately evaluate the efficacy and safety, subjects with moderate to severe MDD are eligible for this study, and subjects with mental disorder other than MDD are excluded from this study.

6.2.2 Study Design

This study is designed based on Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of PFSB/ELD dated 16 November 2010).[3]

A double-blind, randomized, placebo-controlled study is designed for adequate evaluation of the drug efficacy and safety and is used as a standard study design for antidepressants. The use of placebo has continued to be a subject of discussion on the grounds of possible worsening of depressive symptoms or potential increase in suicidal risk; however, there is no evidence that assignment to placebo results in permanent harm or an increased risk of committing suicide. Subjects at significant risk of suicide are ineligible for this study. Furthermore, suicidal risk of a subject will be assessed using C-SSRS at every visit.

The subjects will be informed about the possibility of receiving placebo, the possible risks with placebo, and their right to withdraw from the study at any time. To a subject who discontinues the study, any other appropriate treatment will be provided based on the investigator's decision.

In addition, a 1-week placebo lead-in period is set prior to the double-blind treatment period to exclude subjects who highly respond to placebo from the study, and thereby subjects who have significantly improvement or aggravation of depressive symptoms during the placebo lead-in period will be excluded.

Justification for sample size is described in Section 13.3.

6.2.3 Doses

In overseas phases II and III studies, the efficacy of Lu AA21004 at doses of 5, 10 and 20 mg/day was shown, with no significant safety concerns. In addition, based on the results of meta-analyses in 11 placebo-controlled, double-blind, short-term studies, the differences of the mean changes from baseline in the MADRS total score at Week 6 or 8 between the Lu AA21004 5, 10 or 20 mg group and the placebo group were -2.3 ($p = 0.007$), -3.6 ($p < 0.001$), and -4.6 ($p < 0.001$), respectively, showing that the difference with the placebo group became greater with the dose increase of Lu AA21004.

In Study CCT-002 for subjects with MDD including Japanese, Lu AA21004 was safe up to a dose of 20 mg/day. And although no statistically significant differences had been demonstrated in the efficacy between the Lu AA21004 groups and the placebo group, the efficacy of Lu AA21004 in the 10 and 20 mg groups was grater than in the placebo group in both overall population and Japanese population.

From the results of previous Japanese and overseas studies above, since there were no significant safety concerns about Lu AA21004 up to a dose of 20 mg/day and Lu AA21004 at doses of 10 and 20 mg/day is expected to be effective, these 2 doses will be assessed in this study.

6.2.4 Endpoints

MADRS or HAM-D is recommended for efficacy assessments in Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of PFSB/ELD dated 16 November 2010).[3] Based on the guideline, the MADRS, which is designed to be sensitive to the changes in severity of core symptom of depression, will be used for the primary endpoint evaluation [6], and the HAM-D for the secondary endpoint evaluation in this study.[7] CGI-S and CGI-I will be used to assess subject's overall severity and improvement of depression.[8] In addition to these objective assessments of symptoms, SDS will be used in this study to assess patient's subjective treatment effects on social function disabilities due to depression.[9]

Results of overseas studies of Lu AA21004 showed that Lu AA21004 improved cognitive functions in subjects with MDD. In this study, DSST and PDQ-5 will be used to explore the effect of Lu AA21004 on cognitive functions in Japanese subjects with MDD.

Safety and tolerability of Lu AA21004 will be evaluated by monitoring of AEs, vital signs, weight, clinical laboratory tests, ECGs, and physical examinations. In addition with these safety

evaluations, since it is important to assess suicidal risk for clinical evaluation of antidepressants, suicidal risk will be assessed using C-SSRS at each visit in this study.[10][11]

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject suffer from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x).
4. The subject is a man or a woman aged 20 to 75 years (both inclusive) at the time of informed consent.
5. The reported duration of the current major depressive episode is 3 to 12 months (both inclusive) at the start of screening period.
6. The subject has a MADRS total score ≥26, a HAM-D17 total score ≥18, and a CGI-S score ≥4 at the start of screening period, the start of placebo lead-in period and the start of double-blind treatment period.
7. A female subject of childbearing potential* who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent to the end of the follow-up period.

* Definitions of a female subject of childbearing potential are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities of pregnancy are defined in Section 9.1.14 Pregnancy.

<Justification for Inclusion Criteria>

Criteria 1 and 2 were set as standard requirements to conduct clinical studies.

Criterion 3 was set to identify the target disease and diagnostic criteria for this study. In addition, in order to reduce the possibility of enrolling subjects who highly respond to placebo, the primary diagnosis was set as recurrent MDD.

Criterion 4 was set for the lower limit of age as 20 years old because it was the adult age under the Civil Code. In addition, since the previous pivotal phase II or III studies set 75 years old as the upper limit of age, the upper limit of age in this study was set as 75 years old in the light of the possible comparison with the previous data.

Criterion 5 was set to enroll subjects who had persistent major depressive episode for at least 3 months in consideration of diagnostic certainty. The upper limit of episode duration was set as 12

months since, in general, subjects with chronic depressive symptoms are highly likely to have other concurrent mental disorder and the low possibility that the depressive symptoms would completely disappear with antidepressant drugs.

Criterion 6 was set to enroll subjects with moderate or more severe MDD in severity as eligible for this study.

Criterion 7 was set with respect to the safety risk related to pregnancy in female subjects.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has any following current or past history of psychiatric disorder and/or neurological disorder:
   - Any current psychiatric disorder other than MDD as defined by DSM-IV-TR (To be assessed by Mini International Neuropsychiatric Interview: MINI). A subject who exhibits symptoms of anxiety is eligible unless the subject fulfills the diagnostic criteria for a current anxiety disorder per DSM-IV-TR.
   - Current diagnosis or history of manic, mixed or hypomanic episode, MDD with psychotic features, schizophrenia or any other psychotic disorder (including substance-related mental disorders, or mental disorders due to a general medical condition) as defined by DSM-IV-TR.
   - Current diagnosis or history of any substance-related disorder (except nicotine and caffeine-related disorders) as defined by DSM-IV-TR.
   - The subject with a positive urine drug screening result at the start of screening period or the start of placebo lead-in period. In case that a subject showed positive test result at the start of screening period because the test was conducted before washout of pretreatment drug, the subject is eligible as long as he/she shows negative result at the start of placebo lead-in period.
   - Presence or history of any clinically significant neurological disorder (including epilepsy).
   - Any neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).
   - Any DSM-IV-TR axis II disorder.
2. The subject has the current or previous major depressive episode which were considered by the investigator to have been resistant to 2 or more adequate antidepressants treatments of at least 6 weeks duration each at sufficient doses.

3. The subject has received any augmentation therapy (e.g. lithium, T3/T4, lamotrigine, sodium valproate, carbamazepine, additional atypical antipsychotic, or concomitant use of other antidepressant, etc.) for the current major depressive episode.
4. In the opinion of the investigator, the subject has experienced significant number of major depressive episodes in the past, and is suspected of disease other than MDD.
5. In the opinion of the investigator, the subject has experienced the first major depressive episode at his/her young age, and is suspected of disease other than MDD.
6. The subject has a MADRS total score at the start of double-blind treatment period that has improved or aggravated by 25% or more from the score at the start of placebo lead-in period.
7. The subject is significantly non-compliant with the study medication in the placebo lead-in period; e.g., not taking the study medication for 6 or more consecutive days.
8. The subject has received electroconvulsive therapy, vagus nerve stimulation, or repetitive transcranial magnetic stimulation therapy within 6 months prior to the screening period, or plans to initiate such therapy during the study.
9. The subject is receiving cognitive-behavioral therapy or psychotherapy at the time of informed consent, or plans to initiate such therapy during the study.
10. The subject is at significant risk of suicide or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS at the start of screening period, the start of placebo lead-in period or the start of double-blind treatment period, or has attempted suicide within 6 months prior to the start of screening period.
11. The subject has experienced any environmental change (e.g. temporary retirement, returnment, change of residence) considered by the investigator to have the potential to impact on the efficacy evaluation, or plans such environmental changes during the study.
12. The subject is currently receiving drug therapy for thyroid dysfunction.
13. The subject is currently receiving hormonal therapy for gynecological disease.
14. The subject has taken excluded medications during the protocol-specified period, or will require to take excluded medications during the study.
15. The subject has previously received vortioxetine.
16. The subject has received study medication in a previous clinical study of Lu AA21004 (including this study).
17. The subject has a clinically significant chronic liver disease.
18. The subject has a history of severe allergy or hypersensitivity to drugs.
19. The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, neoplastic, skin and subcutaneous tissue disorders, eye disorders, or metabolic disturbance.

20. The subject has clinically significant abnormal vital signs as determined by the investigator at the start of screening period, placebo lead-in period, or double-blind treatment period.
21. The subject has clinically significant abnormal ECG as determined by the investigator, at the start of the screening period, placebo lead-in period, or double-blind treatment period.
22. The subject has clinically significant abnormal findings of clinical laboratory tests as determined by the investigator, or has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN at the start of screening period or placebo lead-in period.
23. If female, the subject is pregnant or lactating.
24. The subject has a disease or takes medications that could, in the opinion of the investigator, interfere with the evaluation of the safety, tolerability, or efficacy.
25. The subject is, in the opinion of the investigator, unsuitable for this study for any other reason.

<Justification for Exclusion Criteria>

Criteria 1, 4, and 5 were set to exclude subjects or the possible subjects with concurrent mental or neurological disorder other than MDD and to adequately evaluate the efficacy and safety for the target disease.

Criterion 2 was set to exclude subjects or the possible subjects with refractory major depression and include adequate subjects for the evaluation of drug effect.

Criterion 3 was set to exclude subjects who have received augmentation therapy and include adequate subjects for the evaluation of drug effect since subjects who are required to receive augmentation therapy may have refractory major depression or concurrent mental or neurological disorder other than MDD.

Criterion 6 was set to exclude subjects who highly respond to placebo and include adequate subjects for the evaluation of drug effect. Subjects who abruptly worsen their symptoms in a short time are also excluded from the study in consideration of the appropriateness of drug effect evaluation and the safety of subjects.

Criterion 7 was set because it influences the evaluation in the placebo lead-in period.

Criteria 8, 9, 11 to 13 were set because they could influence the evaluation of efficacy.

Criteria 10, 17 to 22 were set with respect to the safety of subjects.

Criteria 14 and 24 were set because they could influence the evaluation of efficacy and safety.

Criterion 15 was set because the bias toward Lu AA21004 based on their treatment experience could influence the evaluation of the efficacy and safety.

Criterion 16 was set to avoid duplicated evaluation of subjects.

Criterion 23 was set with respect to the safety risk for pregnant women, fetuses, neonates, or nursing infant.

Criterion 25 was set to exclude subjects who are considered to be unsuitable for this study for any other reason.

7.3 Excluded Medications and Treatments

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Any treatments for depression other than the study medication, including electroconvulsive therapy, vagus nerve stimulation, repetitive transcranial magnetic stimulation, cognitive-behavioral therapy or psychotherapy are prohibited during the study.

A list of prohibited/restricted concomitant medication is provided in Table 7.a.

Table 7.a List of Prohibited or Restricted Concomitant Medications

Drug Class	Comments or Exceptions
84 days before the start of double-blind treatment period (Day -84) through the end of double-blind treatment period (Visit 8) or early termination	
(1) Any investigational drug	
Start of the screening period (Visit 1) through the end of double-blind treatment period (Visit 8) or early termination	
(2) Antidepressants	Including MAOIs.
(3) Anxiolytics (tranquilizers)	Including benzodiazepines.
(4) Hypnotics	Non-benzodiazepines (zolpidem, zopiclone, and eszopiclone) are allowed. However, use of these drugs should be kept to the minimum necessary, and use for 2 or more consecutive days and use at the night before a study visit are NOT allowed. In addition, the type and dose of non-benzodiazepines should NOT be changed from the start of placebo lead-in period (Visit 2) to the end of double-blind treatment period (Visit 8) or early termination.
(5) Antipsychotics	Depot antipsychotics are prohibited within 6 months prior to the start of double-blind treatment period.
(6) Mood stabilizers	Including lithium, valproate, valpromide.
(7) Psychoactive herbal remedies/supplements	Including St. Johns Wort, kava kava, valerian, ginkgo biloba.
(8) Psychotropic agents not otherwise specified	Including tryptophan, melatonin, and dopamine agonists.
(9) Analeptics	
(10) Anti-ADHD	
(11) Anti-Alzheimer's disease	
(12) Anticonvulsants	
(13) Anti-Parkinson’s disease	
(14) Erectile dysfunction drugs	
(15) Anorexics	
(16) Antimigraines	

(17) Antiemetics/antinauseants	Including dopamine antagonists. Only phosphoric acid preparations, bismuth and cola syrup are allowed.
(18) Interferon	
(19) Systemic steroids	Oral preparation and injection are NOT allowed.
(20) Antibiotics	Rifampicin (oral preparation and injection) is NOT allowed.
Start of the placebo lead-in period (Visit 2) through the end of double-blind treatment period (Visit 8) or early termination	
(21) Antiarrhythmics of class Ia, Ic	
(22) Antiulcer drugs	Omeprazole, cimetidine, and sulpiride are NOT allowed.
(23) Anticoagulants/antiplatelet treatment	Including low dose of aspirin as antiplatelet treatment. Low-molecular weight heparins are allowed as needed.
(24) Antidiarrheal agents	Loperamide, bismuth, and kaolin preparations are allowed.
(25) Antihistamines	Loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine are allowed.
(26) Antineoplastics	
(27) Hormones	Chronic use for contraception or treatment of benign prostatic hyperplasia are allowed.
(28) Hypoglycemic agents	Chronic use is allowed.
(29) Insulin	Chronic use is allowed without major change of dose or administration.
(30) Calcium antagonist	Chronic use is allowed without major change of dose or administration.
(31) Narcotic analgesics	Topical administration including for dental use is allowed.
(32) NSAIDs	Episodic use is allowed. Selective COX-2 inhibitors, acetaminophen, and topical NSAIDs are allowed.
(33) Cough/cold agents	Episodic use is allowed. However, chronic use of preparations containing ephedrine, pseudoephedrine, and codeine are NOT allowed for more than 1-week treatment.

MAOI = monoamine oxidase inhibitor, ADHD = attention deficit hyperactivity disorder,
NSAIDs = nonsteroidal anti-inflammatory drugs, COX-2 = cyclooxygenase-2

<Justification for Prohibited or Restricted Concomitant Medications>

(1) was set since other investigational drug could influence the evaluation of the efficacy and safety.

(2) was set since antidepressants could influence the evaluation of the efficacy. Especially, concomitant use of monoamine oxidase inhibitors (MAOIs) was prohibited because concomitant use of MAOIs could enhance serotonin action and influence the evaluation of the efficacy, and because the safety of subjects should be ensured.

(3) was set since anxiolytics (tranquilizers) could improve anxiety which was known to an accompanying symptom of depression and influence the evaluation of the efficacy.

(4) was set since hypnotics could improve insomnia which was known to an accompanying symptom of depression and influence the evaluation of the efficacy. Concomitant use of non-

benzodiazepines was allowed as needed because the extent of anxiolytic and carry-over effects of non-benzodiazepines was relatively weak, and thus these effects had only a small influence on efficacy evaluation.

(5) to (13) were set since these drugs had psychotropic activity or central nervous effects and could influence the evaluation of the efficacy.

(14) was set since erectile dysfunction drugs could improve sexual dysfunction and could influence the evaluation of the efficacy and safety.

(15) was set since anorexics influence the appetite assessment related to depression.

(16) and (17) were set since antimigraines and antiemetics/antinauseants could act on serotonin receptors and influence the evaluation of the efficacy and safety. Especially, concomitant use of antiemetics/antinauseants was prohibited because adverse events associated with the study medication should be appropriately evaluated.

(18) and (19) were set since interferon and systemic steroids could induce depressive symptoms and influence the evaluation of the efficacy.

(20) was set since antibiotics could decrease the plasma drug concentration by inducing drug metabolic enzymes and influence the evaluation of the efficacy and safety.

(21) and (22) were set since antiarrhythmics of class Ia, Ic, and antiulcer drugs could increase the plasma drug concentration by inhibiting drug metabolic enzymes and influence the evaluation of the efficacy and safety

(23) was set since concomitant use of anticoagulants/antiplatelet treatment drugs could enhance bleeding tendency.

(24) was set since gastrointestinal adverse events associated with the study medication should be appropriately evaluated.

(25) was set since drowsiness, an adverse drug reaction of antihistamines, could attenuate insomnia, which was known to an accompanying symptom of depression and influence the evaluation of the efficacy. Concomitant use of only loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine, which are considered to cause less drowsiness, was allowed.

(26) was set since antineoplastics could influence the evaluation of the efficacy and safety.

(27) and (28) were set since hormones and hypoglycemic agents could influence the evaluation of the efficacy and safety. However, chronic use of these drugs at a certain dose was allowed as having little influence on the evaluation.

(29) and (30) were set since insulin and calcium antagonists could induce depressive symptoms. However, chronic use of insulin or calcium antagonist at a certain dose was allowed as having little influence on the efficacy evaluation.

(31) was set since analgesic action of narcotic analgesics could influence the evaluation of the efficacy. However, topical administration such as for dental use is allowed since narcotic

analgesics have only a small influence on the evaluation.

(32) was set since the concomitant use of NSAIDs could cause upper gastrointestinal bleeding. However, the episodic use of NSAIDs as well as the concomitant use of selective COX-2 inhibitors, acetaminophen, and topical NSAIDs was allowed since these treatments had a relatively lower effect on gastrointestinal adverse events.

(33) was set since some cough/cold agents increase the serotonin concentration of the central nervous system. Concomitant use of ephedrine and codeine for more than 1 week was not allowed due to their addictiveness.

7.4 Diet, Fluid, and Activity Control

The investigator or study collaborator should instruct subjects on the following items:

1. The subject must be punctual for visit, undergo physical examination and predefined examinations. If the subject cannot visit, he/she should inform the investigator or study collaborator as soon as possible.
2. If the subject experiences a worsening of conditions on any day the site visit is not scheduled, he/she should inform the investigator or study collaborator of the worsening by telephone or other manners as soon as possible and seek instructions.
3. The subject must take the study medication as instructed by the investigator. If the subject is noncompliant with study treatment, he/she should inform the investigator or study collaborator of the noncompliance with treatment at visit. The subject must return unused study medication and study medication sheets at visit.
4. The subject must not take any medications including over-the-counter products other than medications as instructed by the investigator without advance consulting (except for emergency).
5. If the subject consults other medical institution from the time of informed consent to the end of the follow-up period, notify the physician of medical institution of the subject's participation in this study.
6. If the subject consults other medical institution from the time of informed consent to the end of the follow-up period, notify the investigator of the circumstances and therapy.
7. The subject must visit the site under fasted conditions at Visits 2, 3 and 8 or Early Termination Visit. For visits serum chemistry test is scheduled, the subject visits the site under fasted conditions wherever possible.
8. Female subject of childbearing potential who is sexually active with a nonsterilized male partner must routinely use adequate contraception from the time of informed consent to the end of the follow-up period.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the case report form (eCRF) using the following categories. For the subject who prematurely discontinues the study before entry into the placebo lead-in period or randomization, refer to Section 9.1.18 or 9.1.20, respectively.

1. **Pretreatment event (PTE) or adverse event (AE)**
   The subject has experienced a pretreatment event (PTE) or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

2. **Liver function test (LFT) abnormalities**
   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study medication treatment:

   – alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or

   – ALT or AST >5 × ULN and persists for more than 2 weeks, or

   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or

   – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. **Significant protocol deviation**
   The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. **Lost to follow-up**
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

5. **Voluntary withdrawal**
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. (i.e., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category.)

6. **Study termination**
   The sponsor, IRB, or regulatory agency terminates the study.

7. **Pregnancy**
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.

8. **Lack of efficacy**
   The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.

9. **Medication noncompliance**
   The subject did not take the study medication for 6 or more consecutive days.

10. **Other**
    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5.1 Additional Guidance for Withdrawal Criteria

Any signs of suicidal risk will be assessed throughout the study by C-SSRS and MADRS assessments and clinical judgment of the investigator. If the subject has a significant risk of suicide in the opinion of the investigator, or the subject has the MADRS score of ≥5 on item 10 (suicidal thoughts), the subject will prematurely discontinue the study.

If subject's underlying diseases become exacerbated, and the investigator concludes any excluded medications or treatment is required, the subject will prematurely discontinue the study.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

Table 8.a Study Medication

Name	Active Substance	Dosage Form	Strength	Manufacture
Lu AA21004 tablet	1-[2-(2,4-dimethyl-phenyl sulfanyl)-phenyl]-piperazine, hydrobromide	Indistinguishable round biconvex tablets	10 mg or 20 mg	Takeda Pharmaceutical Company Limited
Placebo tablet	None		–	

The study medications are identical in appearance.

As for the study medications for the placebo lead-in period, 14 tablets of placebo are packaged in 1 press-through pack (PTP) sheet, and a single sheet is enclosed in an outer carton. The 1 outer carton (including 7 days' spare tablets) will be provided to each subject in the placebo lead-in period.

As for the study medications for the double-blind treatment period, 14 tablets of Lu AA21004 or placebo are packaged in 1 PTP sheet. For Week 1 in the double-blind treatment period, 1 sheet (including 7 days' spare tablets) is enclosed in an Inner Carton 1, and, for Weeks 2 to 8 in the double-blind treatment period, 5 sheets (including 21 days' spare tablets) are enclosed in an Inner Carton 2. Inner Cartons 1 and 2 are packed together in an outer carton. The 1 outer carton will be provided to each subject in the double-blind treatment period.

The outer carton is labeled with a note that the formulation therein is used for a clinical study and pertinent information of the name and quantity of the study medication, the sponsor's name and address, manufacturing number, and storage conditions.

8.1.2 Storage

The study medications should be stored at room temperature (1°C to 30°C).

The study medication must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. The study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

For the placebo lead-in period, administration of the study medication will be started on the day after Visit 2, and subjects will orally take 1 tablet of placebo once daily.

For the double-blind treatment period, administration of the study medication will be started on the day after Visit 3, and subjects will orally take 1 tablet of Lu AA21004 at a dose of 10 mg or 20 mg or placebo once daily.

The investigator or designee should instruct subjects to take the study medication at the same time, a certain time in the morning to the extent possible, throughout the study. The study medication can be taken under both fed and fasted conditions.

At each visit, subjects will be provided with necessary and sufficient amount of the study medications to be used by next visit by the investigator or designee. The investigator or designee must instruct subjects to bring the all remaining study medication and container (PTP sheets) at each visit.

The dose (tablet count) that will be provided to each group and regimen are shown in Table 8.b.

Table 8.b Dose and Regimen

Treatment Group	Regimen	Tablet Count/Dose		
		Placebo Lead-in Period	Double-blind Treatment Period (Week 1)	Double-blind Treatment Period (Weeks 2 to 8)
Placebo Group	Oral, once daily	Placebo tablet ×1	Placebo tablet ×1	Placebo tablet ×1
Lu AA21004 10 mg/day Group	Oral, once daily	Placebo tablet ×1	Lu AA21004 10 mg tablet ×1	Lu AA21004 10 mg tablet × 1
Lu AA21004 20 mg/day Group	Oral, once daily	Placebo tablet ×1	Lu AA21004 10 mg tablet ×1	Lu AA21004 20 mg tablet ×1

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of the study medication to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. This includes any concomitant medication received at a dose greater than that prescribed to the subject.

All cases of overdose will be documented as AEs on an AE page of the eCRF according to Section 10.2.1, and should be reported as a special interest AE according to Section 10.2.1.3 (with or without associated AEs). Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure in Section 10.2.2.

In the event of an overdose of the study medication, the investigator should take general symptomatic and supportive treatment, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose,

respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive treatment should be conducted.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive the next available medication ID number allocated to each study site. The Medication ID Number will be entered onto the eCRF.

8.3 Randomization Code Creation and Storage

Randomization personnel (a person designated by the sponsor) will generate the randomization code. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The emergency key code administration center will maintain the emergency key code until its breaking for an emergency or completion of database lock of all subjects.

Since analytical results of the plasma concentration may jeopardize maintenance of study blinding, the analytical laboratory will keep the final analytical results and not disclose to a third party until unblinding of the study. The analytical laboratory will report the results to the sponsor after they receive the notification of unblinding of the study. However, the analytical laboratory may disclose the results to the sponsor through a responsible person for randomization before unblinding of the study taking measures to secure the blinding such as reassignment of the medication number so that persons in the laboratory may not identify a subject. The detailed procedure will be specified in the separately created manual for handling of biological specimen for pharmacokinetic analysis.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject.

For unblinding, the investigator may contact the emergency key code administration center and obtain allocation information of the study medication.

The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking, and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

For details of unblinding procedure, refer to the manual for Breaking of Emergency Key Code.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage, and management of study drug created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

A separate informed consent form pertaining to pharmacogenomic research must be obtained prior to collecting a sample for Pharmacogenomic Research for this study (see Section 9.1.16). The provision of consent to research in pharmacogenomics is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, alcohol use, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any mental disorders other than MDD (including dysthymic disorder, generalized anxiety disorder, obsessive-compulsive disorder, as defined by DSM-IV-TR) that resolved within 1 year prior to signing of informed consent. Medical history of MDD (past major depressive episode) to be obtained will include determining whether the subject had MDD according to Section 9.1.4.2.

Medication history information to be obtained includes any medication that stopped prior to signing of informed consent and used for treatment of the current major depressive episode or accompanying symptoms. Name of medication used, dose level, unit, dose frequency, route of administration, and the dates of the initial dose and the last dose must be recorded.

9.1.3 Diagnosis of MDD

Diagnosis of MDD and other psychiatric disorders must be based on DSM-IV-TR criteria. In addition, the Mini International Neuropsychiatric Interview (MINI) must be used as an auxiliary diagnostic tool. MINI is a structured diagnostic interview designed to provide a brief standardized evaluation of major Axis I psychiatric disorders in DSM-IV-TR. The investigator can use the MINI after a training session for diagnosis of MDD. Only the version provided by the sponsor that has been validated in Japanese will be used in this study.

9.1.4 Assessments of Major Depressive Episode

9.1.4.1 Current Major Depressive Episode

The following items will be assessed for the current major depressive episode.

- Start date
- Symptom (Select from 9 symptoms listed below as defined by DSM-IV-TR.)
- Psychotherapy (yes or no)

<Symptoms of Major Depressive Episode>

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of weight in a month), or decrease or increase in appetite nearly every day.

(4) Insomnia or hypersomnia nearly every day.

(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

(6) Fatigue or loss of energy nearly every day.

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

9.1.4.2 Past Major Depressive Episode

The following items will be assessed for past major depressive episode.

- Start date and duration of each past major depressive episode.
- Antidepressant drug treatment for each past major depressive episode (yes or no). If the subject has received an antidepressant drug, category of the drug (select from SSRIs, SNRIs, or other antidepressant drugs.) and duration will be recorded.

9.1.5 Physical Examination Procedure

A physical examination will consist of the following body systems:

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

All subsequent physical examinations should assess clinically significant changes from the examinations prior to first dose.

9.1.6 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height will be collected in centimeters without decimal places, and weight will be collected in kilograms (kg) to 1 decimal place. The BMI will be calculated by the sponsor to 1 decimal place with the formula provided below:

$$\text{Metric: BMI} = \text{weight (kg)}/\text{height (m)}^2$$

9.1.7 Vital Sign Procedure

Vital signs will include body temperature (infra-axillary measurement), sitting blood pressure (resting more than 5 minutes), and pulse (bpm).

9.1.8 Efficacy Evaluation

The efficacy will be evaluated using rating scales (MADRS, HAM-D, CGI-S/I, SDS, DSST, and PDQ-5). These assessments should be performed by the investigator who has sufficient experience in clinical practice of diagnosing and treating MDD and who was approved by the sponsor as a rater in this study. The same rater should, whenever possible, assess the same subject throughout the study.

In principle, the MADRS should be performed first at visits that the above-mentioned multiple rating scales will be performed. Efficacy data using these rating scales should be recorded in eCRF by the next visit of the subject at the latest.

In addition, self-report of depressive symptoms by subjects will be performed using Quick Inventory of Depressive Symptomatology (QIDS-J). For QIDS-J, any sequencing order with other rating scales is allowed. QIDS-J data will not be recorded in the eCRF.

9.1.8.1 Rating and Rating Training for MDD

Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS will be used for a primary efficacy measurement. The MADRS is a depression rating scale consisting of 10 items representing the core symptoms of depression.[6] The MADRS is rated using Structured Interview Guide for MADRS (SIGMA). The rating should be based on a clinical interview with the subject, moving from broadly phrased questions about symptoms to more detailed questions. The rating is performed based on the most severe

condition of the subject during the past 1 week, and each item is rated from 0 to 6. Item 1 and Items 3 to 10 are based on subject report, and Item 2 is based on the observation of the subjects. The rater must decide whether the rating for each item lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). Each item score and the total score of all items should be recorded on the eCRF.

Before the first rating, the investigators (hereinafter referred to as [potential] raters in this section) will attend a MADRS training session. Potential raters will watch and score a recorded MADRS interview (video/DVD). A discussion will follow the training session to achieve alignment among raters on the scoring of each individual item.

The sponsor will qualify the raters who achieve the scoring in the training session, and issue a certificate. No subject may be rated before the rater receives the certificate. For potential raters who cannot attend the training session or who are not qualified in the training session, similar MADRS training will be held in each study sites.

If a rater is changed or added during the course of the study, the newly appointed rater must complete all training requirements satisfactorily and must be approved by the sponsor.

Hamilton Depression Rating Scale (HAM-D)

The HAM-D is a depression rating scale that assesses overall symptoms of depression including somatic symptoms. The rater must rate each item score between 0 to 2/3/4 based on a clinical interview with the subject.[7] The rating should be based on patient's condition during the past 1 week prior to the time of assessment. The HAM-D21 is used for rating, and total score of the first 17 items is used as HAM-D17 total score. Each item score and the HAM-D17 total score should be recorded on the eCRF. Prior to the first rating, potential raters will attend a session on concerns to be addressed for the rating of HAM-D.

Clinical Global Impression Scale (CGI)

The CGI consists of 2 sub-scales: CGI-S and CGI-I.[8] The CGI-S assesses the physician's impression of the subject's current mental disorder state. The rater should use his/her total clinical experience with this subject population and rate the current severity of the subject's mental disorder on a 7-point scale. The CGI-I assesses the subject's improvement (or worsening). The rater is required to assess the subject's condition relative to baseline* on a 7-point scale. In all cases, the assessment should be made independent of whether the rater believes the improvement is study medication-related or not. Each score of CGI-S and CGI-I should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the rating of CGI.

* The start day of the double-blind treatment period (Visit 3) is defined as baseline. However, for the assessment at the start of double-blind treatment period (Visit 3) or early termination visit prior to the start of double-blind treatment period, CGI should be assessed comparing with the score at the start of placebo lead-in period (Visit 2).

9.1.8.2 Social Function Assessment

Sheehan Disability Scale (SDS)

The SDS is a scale that assesses disabilities in 3 social function domains subjectively.[9] The subject self-rates the extent to which his or her work/school, social life/leisure activities, and home life/family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale. The SDS also addresses the number of days the above functions were lost or under-productive due to the symptoms. Each item score should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the rating of SDS.

9.1.8.3 Cognitive Function Assessments

Digit Symbol Substitution Test (DSST)

The DSST is a test battery used for assessment of cognitive functions. In the DSST, subjects are shown 9 digit-symbol pairs and required to pair the same digit and symbol combination. Levels of cognitive functions are assessed by the number of correct symbols (0 to 133 scores) within the time limit. DSST scores should be recorded on the eCRF. Subjects will complete the sample items prior to the actual test, but the results of the sample items should not be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of DSST.

Perceived Deficits Questionnaire (PDQ-5)

The PDQ-5 is a self-report questionnaire by subjects used for assessment of their cognitive functions. PDQ-5 consists of 5 questions and provides an assessment of several domains of cognitive functions: attention, retrospective memory, prospective memory, and planning and organization. Sub-scores of each item score (0 to 4 scores) and the total score of all items should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of PDQ-5.

9.1.8.4 Self-report Assessment of Depressive Symptoms and Assessment Monitoring

Quick Inventory of Depressive Symptomatology (QIDS-J)

The QIDS-J is a basic self-report depression scale, and the partially revised version provided by the sponsor will be used for this study. Subjects will enter the responses to each questions of the QIDS-J into the terminal. The rater should not see the responses and not record them on the eCRF. The responses will be reviewed by the expert who has adequate experience in assessment of depression. Appropriateness of the efficacy evaluation will be monitored by comparing with results of other efficacy evaluation of the relevant subject.

9.1.9 Suicidal Risk Assessments

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical study. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.[10][11] Responses to each question will be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of C-SSRS.

9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through Visit 8 or Early Termination Visit), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF.

9.1.11 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent, except for accompanying symptoms of MDD. This includes clinically significant laboratory, vital sign, ECG, or physical examination abnormalities noted at the first examination after signing of informed consent in the opinion of the investigator. The condition (i.e., diagnosis) should be described.

9.1.12 Procedures for Clinical Laboratory Samples

The items of clinical laboratory tests are shown in Table 9.a. Samples will be collected and handled in accordance with the separate operation manual. For clinical laboratory tests, the maximum volume of blood at any single visit is approximately 10 mL.

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**	
Red blood cells (RBC)	Albumin	Glucose (fasting or non-fasting) [a)]
White blood cells (WBC)	AST	Total protein
Hemoglobin	ALT	Potassium
Hematocrit	γ-GTP	Sodium
Platelets	Alkaline phosphatase	Calcium
Neutrophils	Total bilirubin	Chloride
Eosinophils	Direct bilirubin	Lipids (fasting or non-fasting) [a)]
Basophils	(Conjugated bilirubin)	Triglycerides
Lymphocytes	Creatinine	Total Cholesterol
Monocytes	Creatine kinase	High-density lipoprotein cholesterol
	Blood urea nitrogen (BUN)	Low-density lipoprotein cholesterol (direct measurement)
	Uric acid	
Hormonal Test (Visit 1 only)	**Urinalysis**	
Thyroid stimulating hormone (TSH) [b)]	Protein (qualitative)	Urine pH
Free T_4 [b)]	Glucose (qualitative)	Microscopic examination [c)] (white blood cells, red blood cells, and casts)
	Occult blood (qualitative)	
Pregnancy test (female subjects of childbearing potential only)		
Urine human chorionic gonadotropin (hCG)		
Urine Drug Screening [d)]		
Amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaines, morphines, phencyclidines, and tricyclic antidepressants		

a) Blood will be collected under fasted conditions at Visits 2, 3 and 8 or Early Termination Visit. For other visits, blood will be collected under fasted conditions wherever possible.
b) TSH will be measured at Visit 1, and when TSH value is outside the normal range, free T_4 will be measured. If a clinically significant abnormality of thyroid gland is found based on the results of TSH and free T_4, the subject will be excluded from the study.
c) Microscopic examination will be performed if abnormality is found in any item in urinalysis.
d) If the subject has a positive urine drug result, he/she will be excluded from the study. However, when the subject has a positive urine test result at Visit 1 because the urine test was performed prior to washout of pretreatment drug, the subject is eligible for the study if he/she has a negative drug test result at Visit 2.

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and hormonal test. The local laboratory will perform the pregnancy test and urine drug screening. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-GTP, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. If the ALT or AST remains elevated >3 × ULN on these 2 consecutive occasions, the abnormality should be recorded as a special interest AE (hepatic impairment) by the investigator, and follow

the procedure specified in Sections 10.1.5.2 and 10.2.1.3. After additional examinations and detailed monitoring, the investigator must contact the sponsor for consideration of possible discontinuation of the study medication, discussion of the relevant subject details and possible alternative etiologies.

If subjects experience ALT or AST >3 × ULN and total bilirubin >2 × ULN, the investigator must refer to instructions in Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject and Section 10.2.3 Reporting of Abnormal Liver Function Tests.

9.1.13 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, to the end of the follow-up period, female subjects of childbearing potential (e.g., non-sterilized or premenopausal female subjects) who are sexually active with a nonsterilized male partner must use adequate contraception. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed, and subjects will receive continued guidance with respect to the avoiding pregnancy as part of the study procedures (Appendix A).

At visits when pregnancy tests are performed, subjects must be confirmed of having a negative urine hCG pregnancy test, as well as at the follow-up examination.

9.1.14 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any study medication should be immediately discontinued.

If the pregnancy occurs during administration of active study medication from the start of the study medication in the double-blind treatment period to the end of the follow-up period, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the attachment.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician (obstetrics and gynecology specialist) that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.15 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: RR interval, PR interval, QT interval, QRS interval, and QTcB interval. QTcF interval will be calculated by the sponsor. ECG traces recorded on thermal paper should be photocopied to avoid degradation of trace over time.

9.1.16 Pharmacogenomic Sample Collection

One 5-mL whole blood sample for pharmacogenomics will be collected at the start of placebo lead-in period (Visit 2) or at the earliest possible time during the study from subjects who signed informed consent of pharmacogenomics and entered into the placebo lead-in period for possible exploratory investigation of markers enabling the prediction of drug response.

Pharmacogenomic sample should not be collected from any subject who has received comparable bone marrow transplant or whole blood transfusion within 6 months of any sample collection.

See the separately created procedure for collecting, handling, and storage of pharmacogenomic samples.

9.1.17 Pharmacokinetic Sample Collection and Analysis

9.1.17.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples will be collected in concurrence with blood collection for clinical laboratory tests. The exact date and time of the blood collection and dosing times of the last 2 doses prior to the blood collection will be recorded on the eCRF. Refer to the separately created procedure for collection, handling, and shipping of blood samples.

Since drug concentrations of subjects in the placebo group will not be measured, the assignment personnel will send an operation manual to the central laboratory to identify samples of subjects in the placebo group. Drug concentration data will be reported to the sponsor after unblinding of the study.

9.1.17.2 Bioanalytical Methods

Plasma concentrations of Lu AA21004 and its metabolites (Lu AA34443 and Lu AA39835) will be analyzed with the validated LC/MS/MS method.

9.1.18 Documentation of Screen Failure Prior to Entrance into Placebo Lead-in Period

For all subjects who signed informed consent and prematurely discontinue the study prior to entry into the placebo lead-in period, the investigator should complete the eCRF. The registration center should be contacted as a notification of screen failure prior to entry into the placebo lead-in period.

The primary reason for screen failure prior to entry into the placebo lead-in period will be recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria <specify the reason.>
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify the reason.>
- Study termination
- Other <specify the reason.>

The identification numbers assigned to subjects who prematurely discontinues prior to entry into the placebo lead-in period should not be reused.

9.1.19 Documentation of Study Entrance into Placebo Lead-in Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria at the start of placebo lead-in period are eligible for entrance into the placebo lead-in period.

If the subject is found to be not eligible for the placebo lead-in period, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.20 Documentation of Screen Failure Prior to Randomization

For all subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization, the investigator should complete the eCRF. The registration center should be contacted as a notification of discontinuation after entry into the placebo lead-in period and prior to randomization.

The primary reason for screen failure after entry into the placebo lead-in period and prior to randomization is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria <specify the reason.>
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify the reason.>
- Study termination
- Other <specify the reason.>

The end-of-study evaluation will be performed for all subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization according to Section 9.3.5.

9.1.21 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization and entrance into the double-blind treatment period.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for screen failure on the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring unused study medication containers (PTP sheets)/unused medications to each dispensing site visit. The dates of the initial and last dosing, as well as any details where a subject takes more or less of the study medications than the specified dose, will be recorded on the eCRF.

If a subject is significantly noncompliant with the study medication (e.g., 6 or more consecutive doses missed), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Period

Informed consent must be obtained prior to the initiation of any study procedures.

The examinations/observations/assessments listed below will be performed at the start of screening period (Days -32 to -12; Visit 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting a subject who prematurely discontinues the study prior to entry into the placebo lead-in period.

- Demographics, medical history, and medication history
- Diagnosis of MDD
- Assessments of the major depressive episode
- Physical examination
- Weight and height
- Vital signs

- Concomitant medications
- Concurrent medical conditions
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Urine drug screening
- ECG procedure
- C-SSRS
- PTE assessment
- MADRS
- HAM-D
- CGI-S

9.3.2 Placebo Lead-in Period

The examinations/observations/assessments listed below will be performed at the start of placebo lead-in period (Day -8 ± 3; Visit 2). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects assessed to be eligible will enter the placebo lead-in period. See Section 9.1.18 for procedures for documenting subjects who prematurely discontinue the study prior to entry into the placebo lead-in period.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- Urine drug screening.
- Blood sampling for pharmacogenomics* (subjects who provided written consent only)
- ECG procedure
- C-SSRS
- PTE assessment
- MADRS
- HAM-D

- CGI-S
- SDS
- DSST
- PDQ-5
- QIDS-J
- Dispense of the study medication (for the placebo lead-in treatment)

* Blood sampling for pharmacogenomics will be performed at the start of placebo lead-in period (Visit 2) or at the earliest possible time during the study.

9.3.3 Start of Double-blind Treatment Period/Randomization

The examinations/observations/assessments listed below will be performed at the start of double-blind treatment period (Day -1; Visit 3). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects assessed to be eligible will be randomized according to Section 8.2 and enter the double-blind treatment period. See Section 9.1.20 for documenting subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization.

The examinations/observations/assessments at Visit 3 should be regarded as baseline evaluations.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- HAM-D
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 2).
- SDS

- DSST
- PDQ-5
- QIDS-J
- Randomization
- Dispense of the study medication (for the double-blind treatment [Inner Carton 1])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

9.3.4 Double-blind Treatment Period

Visit 4

The examinations/observations/assessments listed below will be performed at 1 week after the start of double-blind treatment period (Day 7 ± 1; Visit 4).

- Vital signs
- Concomitant medications
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- DSST
- PDQ-5
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 5

The examinations/observations/assessments listed below will be performed at 2 weeks after the start of double-blind treatment period (Day 14 ± 3; Visit 5).

- Vital signs
- Concomitant medications
- C-SSRS

- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 6

The examinations/observations/assessments listed below will be performed at 4 weeks after the start of double-blind treatment period (Day 28 ± 3; Visit 6).

- Weight
- Vital signs
- Concomitant medications.
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Pharmacokinetic sampling
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 7

The examinations/observations/assessments listed below will be performed at 6 weeks after the start of double-blind treatment period (Day 42 ± 3; Visit 7).

- Vital signs
- Concomitant medications
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

9.3.5 End of Double-blind Treatment Period or Early Termination

The examinations/observations/assessments listed below will be performed at 8 weeks after the start of double-blind treatment period (Day 56 ± 3; Visit 8) as evaluation at the end of double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period will be requested to visit the study site for early termination examinations/observations/assessments within 7 days after the day of study discontinuation wherever possible.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- Pharmacokinetic sampling (not performed at early termination)
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- HAM-D
- CGI-S

- CGI-I*
- SDS
- DSST
- PDQ-5
- QIDS-J
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

* The CGI-I score will be assessed comparing with that at Visit 3. However, at early termination prior to Visit 3, the CGI-I score will be assessed by comparing with that at Visit 2.

For all randomized subjects, the investigator must complete the End of Study eCRF page.

After evaluation at the end of double-blind treatment period or early termination, standard therapy may be performed as needed.

9.3.6 Follow-up Period

A safety follow-up assessment will be conducted at 12 weeks after the start of double-blind treatment period (Day 84 ± 5). For subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period, the follow-up assessments will be made 28 ± 5 days after the last dose of the study medication. The follow-up assessments may either be conducted as a visit to the site or as a telephone contact. In the follow-up, the following will be assessed: outcomes of AEs continuing at Visit 8 or early termination visit, new SAEs developing during the follow-up period, and special interest AEs will be assessed. Female subjects of child-bearing potential will be asked to confirm whether they are pregnant or not.

9.3.7 Post Study Care

The study medication will not be available upon completion of the subject’s participation in the study.

9.4 Biological Sample Retention and Destruction

Samples of 5-mL whole blood collected for pharmacogenomics will be stored frozen at the pharmacogenomic specimen storage facility (see the contact listed in the attachment 1; hereinafter referred to as specimen storage facility).

The collected samples will be retained for 20 years from the day when a first pharmacogenomic sample was collected during the study.

When subjects request disposal of a stored sample during the retention period, the site will ask the specimen storage facility to destroy the sample via the sponsor according to the procedure. The specimen storage facility will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents

(including medical records) have been destroyed which could identify the subject, and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when pharmacogenomic investigation has been conducted, the remaining sample will be destroyed and the results of pharmacogenomic investigation of the anonymized subject will be retained by the sponsor.

The sponsor will build a management system required for protection of the subject's personal information, define standards for collecting, storage, and destruction of samples, and prepare appropriate procedures.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation).

A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Of pre-existing conditions (present at the time of signing of informed consent), events that are considered accompanying symptoms of MDD should NOT be recorded as concurrent medical conditions, PTEs, or AEs.
- Other pre-existing conditions are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences an abnormality (e.g., internal bleeding due to blood sampling) associated with the baseline evaluations, the abnormality should be recorded as a PTE and recorded on eCRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). The investigator should ensure that the event term recorded captures the change in the condition (e.g., "worsening of hypertension").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, the investigator should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, the investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. The investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. The investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedures is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures (e.g., cosmetic surgery) performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- All cases of overdose with any medication, including the case without manifested side effects, are considered AEs and will be recorded on the AE page of the eCRF. In addition, cases of overdose will be reported as special interest AEs.

Suicidality events:

- A completed suicide is always captured as an SAE based on its fatal outcome. Furthermore, active suicidal behavior such as suicidal ideation with a specific plan and suicide attempt will also be collected as an SAE.
- Unless the event in question meets the definition of "serious," suicidal thoughts or suicidal ideation without a specific plan or action will be collected as a non-serious AE in accordance with the standard AE reporting requirements.
- A subject who presents with self-mutilation should be asked by the investigator to clarify whether the subject was attempting suicide. If the subject was attempting suicide, the behavior will be collected as an SAE, and the specific suicidal behavior (e.g., wrist cutting) will be recorded in the eCRF. If the subject was not attempting suicide, the behavior will be collected as a non-serious AE in accordance with the standard AE reporting requirements.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.*
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

* The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including seizure and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial lung disease)
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death
	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxin shock

The following events are also to be considered SAEs.

- Completed suicide
- Active suicidal ideation
- Active suicidal behavior such as suicide attempt
- Self-injury with suicide attempt

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) is 1 of scientific and medical concern specific to the compound or program. In this study, skin reaction, allergic reaction, hepatic impairment, and overdose are defined as special interest AEs. Ongoing monitoring and communication by the investigator to Takeda may be appropriate, and if the events occur, they will be reported according to Section 10.2.1.3. Such events may require further investigation in order to characterize and understand them.

10.1.5.1 Skin and Allergic Reaction

When the causal relationship between rash or allergic reaction and the study medication is assessed as probable or possible, rash or allergic reaction will be reported as a special interest AE according to Section 10.2.1.3 after the nature and the site are characterized. When the causal relationship between rash or allergic reaction and the study medication is assessed as not related, rash or allergic reaction is not required to be reported as a special interest AE.

When rash or allergic reaction develops, the subject should be adequately examined for any clinical features that may suggest the development of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome (SJS). In addition, the subject should be monitored for the appearance of any of the following signs:

a) Involvement of mucous membrane or the conjunctiva

b) Development of skin pain

c) Urticaria, blistering, or other types of skin lesions

d) Angioedema

If a subject presents with symptoms of a systemic reaction (e.g., generalized rash), or signs of severe rash, or if it is clinically necessary, the following laboratory parameters should also be investigated and monitored accordingly: complete blood count with differentials, liver and renal function tests, and urinalysis. If deemed necessary by the investigator, subjects should be received examination by a dermatologist, and photographs of the skin rash and/or skin biopsies will be obtained as needed.

10.1.5.2 Hepatic Impairment

If a subject has ALT or AST >3 × ULN, and follow-up laboratory tests (see Section 9.1.12) also shows ALT or AST >3 × ULN, it should be reported as a special interest AE according to Section 10.2.1.3. In addition, the relevant subject details and possible alternative etiologies other than the study medication should be investigated.

If the abnormality falls under a drug-induced liver function abnormality that may lead to severe hepatic impairment (see Section 10.2.3), it should also be reported as an SAE.

10.1.5.3 Overdose

For overdose, refer to Section 8.1.4. All cases of overdose will be documented as AEs on an AE page of the eCRF and should be reported as special interest AEs according to Section 10.2.1.3 (with or without associated adverse events).

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Probable:	An AE that has a strong temporal relationship to the study medication(s), or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
Possible:	An AE that has a suggestive temporal relationship to the study medication(s), and an alternative etiology is equally or less likely.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of the study medication(s) or that can reasonably be explained by other factors, such as underlying diseases, concurrent medical conditions, concomitant drugs and concurrent treatments (that is, there is no causal relationship between the study medication and the AE).

An AE is considered causally related to the use of the study medication when the causality assessment is *probable* or *possible*.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs. The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of AEs/PTEs will be determined based on the criteria described below.

AE/PTE	Start Date
Signs, symptoms, and diseases (diagnosis)	Date when the subject or the investigator first notices the sign or symptom of the AE
Asymptomatic disease	Date when a definite diagnosis is determined based on the results of diagnostic testing. Even if obsolete findings are indicated based on the test findings or the approximate time of onset can be estimated, the date when a definite diagnosis is made should be recorded.
Worsening of concurrent medical conditions or PTEs	Date when the subject or the investigator first notices worsening of the disease or symptom.
Normal in the initial assessment after signing of informed consent but abnormal in the subsequent assessment (for PTEs) Abnormal in the assessment after the start of the study medication (for AEs)	Date when the test is performed in which a clinically significant abnormal test value is observed
Abnormal in the initial assessment after signing of informed consent and has worsened in the subsequent assessment (for PTEs) Abnormal in the assessment at the start of the study medication and has worsened in the subsequent assessment (for AEs)	Date when the test is performed in which a medically significant elevation, reduction, increase or decrease in clinical laboratory test values is observed

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The AE/PTE not determined to have resolved at the end of the study is assessed as ongoing

10.1.11 Frequency

Episodic AEs/PTEs (e.g., constipation, diarrhea, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Medication

The action taken for the study medication is classified and defined as follows:

Drug withdrawn	The study medication is stopped due to the particular AE (including withdrawal at the subject's discretion).
Dose not changed	The dose is not changed even after the occurrence of the particular AE. This shall apply in case the study medication is stopped due to another AE. This shall also apply, for example, in case the study medication is stopped for any reason other than intervention for the particular AE, such as the subject's negligence.

Unknown	For example, attempts to contact the subject are unsuccessful and the course of the particular AE after the start date cannot be followed.
Not Applicable	For example, the study medication has already been completed or stopped before the onset of the particular AE.

10.1.13 Outcome

The outcome of AEs/PTEs is classified as follows:

Category	Assessment Criteria
Recovered/Resolved	• The symptom or finding has disappeared or resolved. • The abnormal laboratory value has improved to the normal range or to the level at baseline (for AEs) or at the first assessment after signing of informed consent (for PTEs).
Recovering/Resolving	• The intensity is lowered by at least 1 grade. • The symptom or finding has almost disappeared. • The abnormal laboratory value has improved, but not to the normal range or the level at baseline (for AEs) or at the first assessment after signing of informed consent (for PTEs). • The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (no need to record the date of death).
Not recovered/not resolved	• There is no change in the symptom, finding, or laboratory value. • The intensity of the symptom, finding, or laboratory value on the last day of the observed period has got worsen than when it started. • An irreversible congenital anomaly. • The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" AE/PTE (no need to record the date of death).
Resolved with sequelae	• The subject recovered from an acute AE/PTE but was left with impairment that interferes with the subject's daily life.
Fatal	• There is a direct relationship between the death and the AE/PTE. • The direct relationship indicates that the AE/PTE caused or apparently contributed to the death. • The outcome of another AE/PTE reported in the same subject that is not determined (considered or estimated) as the cause of the death is not assessed as "fatal." • If the outcome is "fatal," the date of death should be recorded.
Unknown	• The course of the AE/PTE after the start date cannot be followed up as specified in the protocol due to hospital change or residence change.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication in the

placebo lead-in period. For subjects who discontinue prior to the first study medication administration in the placebo lead-in period, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication in the placebo lead-in period. Routine collection of AEs will continue until Visit 8 or Early Termination Visit.

Collection of SAEs or special interest AEs will continue until the end of the follow-up period.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the change (for permanent or irreversible PTEs). Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the change (for permanent or irreversible AEs). All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date
3. Frequency
4. Severity
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (probable, possible, not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs)
8. Outcome of event
9. Seriousness
10. Classification as special interest AEs (Yes or No)

C-SSRS will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. If it is determined that an AE not previously reported has been identified through this follow-up, normal reporting requirements should be applied.

AEs and serious PTEs will be followed up until resolution or until the investigator judges that further follow-up is not necessary.

10.2.1.3 Special Interest AE Reporting

If the special interest AE (refer to Section 10.1.5) occurs through the AE collection period, it should be reported to Safety Information Emergency Call Center, in principle (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The investigator should complete the Rash and Allergic Reaction, Hepatic Impairment or Overdose Form within 10 business days and report to Safety Information Emergency Call Center, in principle. In addition, the investigator should submit to the sponsor the original Rash and Allergic Reaction, Hepatic Impairment or Overdose Form.

The special interest AEs have to be recorded as AEs in the eCRF.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure. PTEs that fulfill the serious criteria described in Section 10.1.4 are also to be considered SAEs and should be reported in the same manner.

The investigator should report the SAEs with information required in the SAE form to Safety Information Emergency Call Center, in principle, within 1 business day of the first onset or subject's notification of the event. The investigator should prepare the completed SAE form within 10 calendar days and submit to Safety Information Emergency Call Center, in principle. In addition, the investigator should submit to the sponsor the original SAE form.

For the report within 1 business day, the information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be also reported to the sponsor if considered related to study participation. Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the investigator must contact the sponsor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests must also be performed (see Section 9.1.12). If the investigator considers that such liver function abnormality cannot be explained by any factor other than the study medication, the event should be reported as a SAE (see Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the detailed report becomes available at a later date, the investigator should complete a follow-up SAE form copy or provide other written documentation and report it immediately to the sponsor or Safety Information Emergency Call Center. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and the head of the study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee (CRO), SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of the study medication or that would be sufficient to consider changes in the administration of study medication or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff (the investigator, subinvestigators, and other study collaborators) in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The investigator must review the eCRFs for completeness and accuracy and must sign the appropriate eCRFs. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs.

- Laboratory test values measured at the central laboratory
- Observed drug concentrations

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail,

and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS), and safety analysis set.

The FAS, which will be used as a primary analysis set for efficacy analysis, is defined as "all subjects who were randomized and received at least 1 dose of the study medication in the double-blind treatment period."

The exact definition of each analysis set is specified in the Data Handling Rules for Statistical Analysis.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Data Handling Rules for Statistical Analysis must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Major background and demographic characteristics will be summarized overall and by treatment group.

13.1.3 Efficacy Analysis

Primary Efficacy Analysis for Primary Endpoint

The primary endpoint for this study is the change from baseline (i.e. at the start of double-blind treatment period) in the MADRS total score after 8 weeks of treatment.

Comparisons between each Lu AA21004 treatment group and the placebo group at Week 8 of the double-blind treatment period will be performed using the FAS based on MMRM analysis of covariance with the change from baseline in the MADRS total score as a dependent variable, and visit, treatment group, visit-by-treatment group interaction and baseline MADRS total score-by-visit interaction as fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom. Holm's step down method will be used to adjust the multiplicity for the comparisons. More specifically, let H_{01}, H_{02} be a family of hypotheses as follows:

H_{01}: $\mu_{Placebo} = \mu_{10\ mg}$

H_{02}: $\mu_{Placebo} = \mu_{20\ mg}$

Then let P_1 and P_2 denote the unadjusted p-values of tests for H_{01} and H_{02}, respectively. Order the p-values from the smallest to the largest, $P^{(1)}$, $P^{(2)}$ and let the corresponding null hypotheses be $H^{(1)}$, $H^{(2)}$. Holm's step-down method proceeds as follows:

Step 1: if $P^{(1)} > 0.025$, retain both null hypotheses $H^{(1)}$ and $H^{(2)}$, and stop. If $P^{(1)} \leq 0.025$, reject null hypothesis $H^{(1)}$ and go to Step 2.

Step 2: if $P^{(2)} > 0.05$, retain null hypothesis $H^{(2)}$. If $P^{(2)} \leq 0.05$, reject null hypothesis $H^{(2)}$.

Secondary Efficacy Analyses for Primary Endpoint

To check the robustness of the results, the same analysis as used for the primary efficacy analysis will be performed using the PPS.

For the FAS, an analysis of covariance (ANCOVA) model with the change from baseline in the MADRS total score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) as a dependent variable, treatment group as a fixed effect and the baseline MADRS total score as a covariate will be applied for comparisons between the placebo group and each Lu AA21004 treatment group.

Analyses for Secondary Endpoints

MADRS response (MADRS response is defined as a ≥50% decrease from baseline in the MADRS total score) and MADRS remission (MADRS remission is defined as the MADRS total score ≤10) after 8 weeks of treatment (LOCF) will be compared between treatment groups using logistic regression analysis including the baseline MADRS total score and treatment groups in the model.

The change from baseline in the HAM-D17 total score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline HAM-D17 total score as a covariate.

The CGI-I score after 8 weeks of treatment (LOCF) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline CGI-S score as a covariate.

The change from baseline in the CGI-S score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline CGI-S score as a covariate.

The change from baseline in the SDS score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline SDS score as a covariate.

The change from baseline in the DSST score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline DSST score as a covariate.

The change from baseline in the PDQ-5 score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline PDQ-5 score as a covariate.

Two-sided tests with significance level at 5% will be used for all statistical tests. Ninety-five percent confidence intervals will be presented along with the P-values.

13.1.4 Pharmacokinetic Analysis

The population pharmacokinetic analysis of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 will be performed using the nonlinear mixed effect model (NONMEM). Pharmacokinetic parameters of individual subjects (e.g., AUC[0-tau], Cavg, Cmax) will be estimated and their correlation with relevant pharmacodynamic parameters (efficacy and tolerability/safety) will be explored. The population pharmacokinetic analysis plan will be prepared separately.

13.1.5 Safety Analysis

AEs

The definition of treatment-emergent adverse events (TEAE) will be described in the statistical analysis plan (SAP). TEAEs will be summarized using the safety analysis set. TEAEs will be coded using the MedDRA and will be summarized by system organ class (SOC) and preferred term (PT). No statistical testing or inferential statistics will be generated.

A subject who has developed a same TEAE more than once will be counted as 1 subject in the severity category corresponding to the maximum severity of the event.

Clinical Laboratory Test, Weight, Vital Signs, and ECG

Summary statistics of observed values and changes at each time point (values at each time point in the double-blind treatment period − baseline) will be calculated for clinical laboratory tests, vital signs, ECG parameters, and weight for each treatment group. Incidences of values that are outside normal ranges and are potentially and clinically significant will be calculated.

C-SSRS

Descriptive statistics of C-SSRS will be calculated at each time point for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A number of subjects planned to be enrolled in this study is 480 (160 per group). Assuming the true mean differences of 3.5 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between each Lu AA21004 group and the placebo group by 2-sample t-test. In addition, assuming the true mean differences of 3.0 for the change from baseline

in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between either the Lu AA21004 10 mg or 20 mg group and the placebo group. These power calculations assume a common standard deviation of 9.5 for the change from baseline in the MADRS total score, with a 2-sided level of 0.025.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, and informed consent documentation. It is important that the investigator, the subinvestigator, and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or signing of informed consent). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug no protocol activities, including the informed consent procedure may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

Regarding pharmacogenomic investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for pharmacogenomics investigations, and a research protocol will require prior approval of the company IRB in Japan.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by the IRB prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent form must be signed and/or sealed, and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign and/or seal using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and/or seal, and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed and/or sealed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. A copy of the signed and/or sealed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

The informed consent form for pharmacogenomic research in the clinical study of Lu AA21004 will be used to explain the pharmacogenomic research to subjects after explanation of the informed consent for the entry into the study. Pharmacogenomic samples will be collected from subjects who have consented to both the study and the pharmacogenomic research.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites (JAPIC-CTI) before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (JAPIC-CTI), as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Nakane Y, Arima K. Cause and Symptom of Depression. The Journal of Practical Pharmacy. 2000;51(2):826-34.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Translated by Takahashi S, Ono Y, Someya T. Igaku-Shoin. 2004.

[3] Guideline for Clinical Evaluation of Antidepressants (Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division; Notification No.1116-1 dated November 16 in 2010) (in Japanese).

[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Translated by Takahashi S, Ono Y, Someya T, Kanba S, Ozaki N, Mimura M, Murai T.. Igaku-Shoin. 2014.

[5] Bialik RJ, Ravindran AV, Bakish D, Lapierre YD., 1995. A Comparison of Placebo Responders and Nonresponders in Subgroups of Depressive Disorder. J Psychiatry Neurosci. 1995;20:265-70.

[6] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

[7] Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278-96.

[8] Guy W. ECDEU Assessment Manual for Psychopharmacology (Revised). Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health, Psychopharmacology Research Branch; 1976. p.193-198

[9] Olfson M, Fireman B, Weissman MM, Leon AC, Sheehan DV, Kathol RG, et al. Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry. 1997;154:1734-40.

[10] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. Am J Psychiatry. 2007;164(7):1035-43.

[11] Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the Assessment of Suicidality in Youth. CNS Spectr. 2007;12(2):156-62.

Appendix A Schedule of Study Procedures

	Screening Period	Placebo Lead-in Period [a]	Double-blind Treatment Period						Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET [c]**	**Follow-up [d]**
Week [b]	-4 to -2	-1	0	1	2	4	6	8/ET [c]	12 [d]
Day [b]	-32 to -12	-8	-1	7	14	28	42	56/ET [c]	84 [d]
Visit Window (Days) [b]	-	±3	0	±1	±3	±3	±3	±3/-	±5
Informed consent	X [e]								
Inclusion/exclusion criteria	X	X [f]	X [f]						
Demographics, medical history, medication history	X								
Diagnosis of MDD	X								
Assessments of major depressive episode	X								
Physical examination	X	X	X					X	
Weight, height [g]	X	X	X			X		X	
Vital signs	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	
Concurrent medical conditions	X								
Clinical laboratory tests [h]	X	X	X			X		X	
Pregnancy test [i]	X	X	X			X		X	(-)
Urine drug screening	X	X							
Pharmacokinetic sampling						X		(X)	
Pharmacogenomic sampling [j]		(X)							
ECG	X	X	X			X		X	
C-SSRS	X	X	X	X	X	X	X	X	
PTE/AE assessment [k]	X	X	X	X	X	X	X	X	(-)
<Assessments with Rating Scales>									
MADRS	X	X	X	X	X	X	X	X	
HAM-D	X	X	X					X	
CGI-S	X	X	X	X	X	X	X	X	
CGI-I [l]			X	X	X	X	X	X	
SDS		X	X					X	
DSST [m]		X	X	X				X	
PDQ-5		X	X	X				X	
QIDS-J		X	X	X	X	X	X	X	
<Clinical Supply>									
Randomization			X						
Dispense study medication [n]		X	X	X	X	X	X		
Drug return/accountability/compliance			X	X	X	X	X	X	

ET = early termination

(a) In the placebo lead-in period, subjects will receive the study medication in a single-blind manner.
(b) The visit day in the double-blind treatment period is defined as Week 0 (Day -1). The day after Day -1 is defined as Day 1. All visit windows are in reference to the date of scheduled visit.
(c) Subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period will be requested to visit the study site for the end-of study examinations within 7 days after the day of study discontinuation, wherever possible, and will be assessed in the same way as at Visit 8 (except for blood sampling for pharmacokinetics).
(d) Safety follow-up assessments will be conducted. For subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period, the follow-up assessments will be made 28 ± 5 days after the last dose of the study medication. The follow-up assessments can either be conducted as a visit to the site or as a telephone contact. In the follow-up, the following will be assessed: outcomes of AEs continuing at Visit 8 (or the end-of study assessments if administration of the study medication is discontinued), new SAEs developed during the follow-up period, and special interest AEs. Female subjects of child-bearing potential will be asked to confirm whether they are pregnant or not.
(e) Informed consent must be obtained prior to the initiation of any study procedure including washout of excluded medications. Informed consent may be obtained prior to the visit window of Visit 1.
(f) Update at Visits 2 and 3.
(g) Height is measured at only Visit 1.
(h) Clinical laboratory tests will be performed under fasted conditions at Visits 2, 3 and 8 or Early Termination Visit, and at other visits wherever possible.
(i) For women of child-bearing potential.
(j) Only for subjects who consent to provide pharmacogenomic samples, separately from consent of participation in the study. Pharmacogenomic samples for analyses will be collected at Visit 2 or thereafter, as soon as possible, during the study.
(k) PTEs will be collected prior to study medication administration in the placebo lead-in period, and AEs will be collected after study medication administration.
(l) The CGI-I score will be assessed by comparison with that at Visit 3. However, at Visit 3 or early termination prior to Visit 3, the score will be assessed by comparison with that at Visit 2.
(m) Subjects will complete the sample items prior to the actual test.
(n) At Visit 2, subjects will be dispensed the study medication for the placebo lead-in period. At Visit 3, subjects will be dispensed the study medication for the double-blind treatment period, Inner Carton 1, and Inner Carton 2 at Visits 4 to 7, with a necessary and sufficient amount of the study medication by next visit.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety, and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications, and responsibilities of individual personnel to the investigator and the study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing, and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of an SAE, immediately notify the director of the site and the sponsor in writing.
11. Determine the need of emergency key code blinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
14. Discuss any proposal from the sponsor including update of the protocol.
15. Notify the director of the site of the end of the study in writing.

Appendix C Detailed Description of Amendments to Text

The following describes changes from the initial protocol.

Page 42, Section 9.1.8.3 Cognitive Function Assessments, Digit Symbol Substitution Test (DSST)

Existing Text

.....*At a start of the placebo lead-in period (Visit 2),* subjects will complete the sample items prior to the actual test, but the results of the sample items should not be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of DSST.

Revised Text

.....Subjects will complete the sample items prior to the actual test, but the results of the sample items should not be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of DSST.

Rationale for Amendment

To clarify to complete the sample items in every DSST assessment.

Page 80, Appendix A Schedule of Study Procedures

Existing Text

	Screening Period	Placebo Lead-in Period [(a)]
Visit Number	**1**	**2**
DSST		X [*(m)*]

Revised Text

	Screening Period	Placebo Lead-in Period [(a)]
Visit Number	**1**	**2**
DSST [**(m)**]		X

Rationale for Amendment

To clarify to complete the sample items in every DSST assessment.

PROTOCOL

<Title>

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Evaluate the Efficacy and Safety of Once Daily Oral Lu AA21004 in Patients with Major Depressive Disorder

<Short Title>

A Phase III Study of Lu AA21004 in Patients with Major Depressive Disorder

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi		
Study Number:	Lu AA21004/CCT-004		
Edition:	Protocol Incorporating Amendment No. 1		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Lu AA21004		
Date:	7 May 2015		

Amendment History

Date	Amendment Number	Region
9 January 2015	Initial Protocol	All Study Sites
7 May 2015	Amendment 1	All Study Sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

Refer to the attachment.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** Lu AA21004	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Evaluate the Efficacy and Safety of Once Daily Oral Lu AA21004 in Patients with Major Depressive Disorder	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: Lu AA21004/CCT-004	**Phase:** 3	

Study Design:

This is a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the efficacy and safety of 8-week treatment of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) in Japanese subjects with major depressive disorder (MDD).

This study consists of a 1- to 3-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week safety follow-up period. Subjects who fulfill all inclusion criteria and none of exclusion criteria at the start of screening period (Visit 1) and at the start of placebo lead-in period (Visit 2) will move into the placebo lead-in period and receive placebo once daily for 1 week in a single-blind manner. Afterwards, these who fulfill all the inclusion criteria and none of the exclusion criteria at the start of double-blind treatment period (Visit 3) will move into the double-blind treatment period and will be randomized in a 1:1:1 ratio to one of the following treatment groups: the placebo group, the Lu AA21004 10 mg/day group or the Lu AA21004 20 mg/day group. Subjects in the placebo group and the Lu AA21004 10 mg/day group will receive placebo and Lu AA21004 10 mg, respectively, once daily from the day after Visit 3 for 8 weeks in a double-blind manner. Subjects in the Lu AA21004 20 mg/day group will receive Lu AA21004 10 mg once daily from the day after Visit 3 for 1 week and thereafter Lu AA21004 20 mg once daily for 7 weeks in a double-blind manner. Subjects in any treatment groups will visit study sites at Week 1, 2, 4, 6 and 8 during the double-blind treatment period for examinations/observations/assessments.

A safety follow-up contact (visit or phone call) will be made 4 weeks after the completion of the double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or the double-blind treatment period will be requested to visit the study site for the end-of study assessments within 7 days after the discontinuation decision is made wherever possible, and will be contacted 4 weeks after the last dose of the study medication for safety follow-up.

Primary Objective:

- To evaluate the efficacy of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.

Secondary Objectives:

- To evaluate the safety and tolerability of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.
- To evaluate the efficacy of Lu AA21004 (10 or 20 mg/day) on cognitive functions after 8 weeks of treatment in Japanese patients with MDD.

Additional Objective:

- To analyze the plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 using population pharmacokinetic analyses.

Subject Population:

Male and female subjects, aged between 20 and 75 years (both inclusive), with recurrent MDD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria.

Number of Subjects:	**Number of Sites:**
Randomized subjects: 480 (160 per group)	Approximately 60 sites
Dose Levels: Placebo lead-in period: Placebo once daily Double-blind treatment period: Lu AA21004 (10 or 20 mg) or placebo once daily	**Route of Administration:** Oral
Duration of Treatment: 9 weeks in total Placebo lead-in period: 1 week Double-blind treatment period: 8 weeks	**Period of Evaluation:** 14 to 16 weeks in total Screening period: 1 to 3 weeks Placebo lead-in period: 1 week Double-blind treatment period: 8 weeks Safety follow-up period: 4 weeks

Main Criteria for Inclusion:

- The subject suffers from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x).
- The subject is a man or a woman aged 20 to 75 years (both inclusive) at the time of informed consent.
- The reported duration of the current major depressive episode is 3 to 12 months (both inclusive) at the start of screening period.
- The subject has a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26, a Hamilton Depression Rating Scale (HAM-D17) total score ≥18, and a clinical global impression scale-Severity (CGI-S) score ≥4 at the start of screening period, the start of placebo lead-in period and the start of the double-blind treatment period.

Main Criteria for Exclusion:

- The subject has any following current or past history of psychiatric disorder and/or neurological disorder:
  - Any current psychiatric disorder other than MDD as defined by DSM-IV-TR (To be assessed by Mini International Neuropsychiatric Interview: MINI). A subject who exhibits symptoms of anxiety is eligible unless the subject fulfills the diagnostic criteria for a current anxiety disorder per DSM-IV-TR.
  - Current diagnosis or history of manic, mixed or hypomanic episode, MDD with psychotic features, schizophrenia or any other psychotic disorder (including substance-related mental disorders, or mental disorders due to a general medical condition) as defined by DSM-IV-TR.
  - Current diagnosis or history of any substance-related disorder (except nicotine and caffeine-related disorders) as defined by DSM-IV-TR.
  - The subject with a positive urine drug screening result at the start of screening period or the start of placebo lead-in period. In case that a subject showed positive test result at the start of screening period because the test was conducted before washout of pretreatment drugs, the subject is eligible as long as he/she shows negative result at the start of placebo lead-in period.
  - Presence or history of any clinically significant neurological disorder (including epilepsy).
  - Any neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).
  - Any DSM-IV-TR axis II disorder.
- The subject has the current or previous major depressive episode which were considered by the investigator to have been resistant to 2 or more adequate antidepressants treatments of at least 6 weeks duration each at sufficient doses.

- The subject has received any augmentation therapy (e.g. lithium, T3/T4, lamotrigine, sodium valproate, carbamazepine, additional atypical antipsychotic, or concomitant use of other antidepressant, etc.) for the current major depressive episode.
- In the opinion of the investigator, the subject has experienced significant number of major depressive episodes in the past, and is suspected of disease other than MDD.
- In the opinion of the investigator, the subject has experienced the first major depressive episode at his/her young age, and is suspected of disease other than MDD.
- The subject has a MADRS total score at the start of double-blind treatment period that has improved or aggravated by 25% or more from the score at the start of placebo lead-in period.
- The subject is at significant risk of suicide or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS at the start of screening period, the start of placebo lead-in period or the start of double-blind treatment period, or has attempted suicide within 6 months prior to the start of screening period.
- The subject has experienced any environmental change (e.g. temporary retirement, returnment, change of residence) considered by the investigator to have the potential to impact on the efficacy evaluation, or plans such environmental changes during the study.
- The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, neoplastic, skin and subcutaneous tissue disorders, eye disorders, or metabolic disturbance.

Main Criteria for Evaluation and Analyses:

Efficacy Endpoints

Primary Endpoint

- Change from baseline (i.e. at the start of double-blind treatment) in the MADRS total score after 8 weeks of treatment

Secondary Endpoints

- MADRS response after 8 weeks of treatment (last observation carried forward [LOCF])
  (MADRS response is defined as a ≥50% decrease in the MADRS total score from baseline).
- MADRS remission after 8 weeks of treatment (LOCF)
  (MADRS remission is defined as the MADRS total score of ≤10).
- Change from baseline in the HAM-D17 total score after 8 weeks of treatment (LOCF).
- Clinical global impression scale-Improvement (CGI-I) score after 8 weeks of treatment (LOCF).
- Change from baseline in the CGI-S score after 8 weeks of treatment (LOCF).
- Change from baseline in the Sheehan Disability Scale (SDS) total score after 8 weeks of treatment (LOCF).
- Change from baseline in the Digit Symbol Substitution Test (DSST) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Perceived Deficits Questionnaire (PDQ-5) score after 8 weeks of treatment (LOCF).

Pharmacokinetic Endpoint

- Plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835.

Safety Endpoints

- Adverse events
- Weight
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Considerations:

Change from baseline (i.e. the start of double-blind treatment period) in the MADRS total score after 8 weeks of treatment is the primary efficacy endpoint. Comparisons between each Lu AA21004 treatment group and the placebo group at Week 8 of the double-blind treatment period will be performed using the full analysis set (FAS) based on Mixed Model for Repeated Measures (MMRM) analysis of covariance with the change from baseline in the MADRS total score as a dependent variable, and visit, treatment group, visit-by-treatment group interaction and baseline MADRS total score-by-time point interaction as fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom. Holm's step-down method will be used to adjust the multiplicity for the comparisons.

Sample Size Justification:

A number of subjects planned to be enrolled in this study is 480 (160 per group). Assuming the true mean differences of 3.5 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between each Lu AA21004 group and the placebo group by 2-sample t-test. In addition, assuming the true mean differences of 3.0 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between either the Lu AA21004 10 mg or 20 mg group and the placebo group. These power calculations assume a common standard deviation of 9.5 for the change from baseline in the MADRS total score, with a 2-sided level of 0.025.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ANCOVA	analysis of co-variance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
Cavg	average plasma concentration at steady state
CGI-I	clinical global impression scale-Improvement
CGI-S	clinical global impression scale-Severity
Cmax	maximum observed plasma concentration
COX	cyclooxygenase
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P-450
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSST	Digit Symbol Substitution Test
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transferase
HAM-D	Hamilton Depression Rating Scale
hCG	Human chorionic gonadotropin
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation
INR	international normalized ratio
LDL	low-density lipoprotein
LOCF	Last Observation Carried Forward
MADRS	Montgomery Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model for Repeated Measures
NaSSA	noradrenergic and specific serotonergic antidepressant
NSAIDs	non-steroidal anti-inflammatory drug
PDQ	Perceived Deficits Questionnaire
PMDA	Pharmaceutical and Medical Devices Agency

PT	Preferred Term
PTE	Pretreatment Event
PTP	press through package
QIDS	Quick Inventory of Depressive Symptomatology
SAE	serious adverse event
SDS	Sheehan Disability Scale
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	selective serotonin reuptake inhibitor
SUSARs	Suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TSH	thyroid-stimulating hormone
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Lu AA21004 (generic name: vortioxetine hydrobromide) is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and 5-HT transporter (5-HTT) inhibitor. This novel antidepressant with a different profile from existing medications has been under development in Japan and overseas. As of December 2014, Lu AA21004 has been approved for marketing as a drug for the treatment of MDD in countries including the U.S., Europe and Australia.

Depression is a mental disease mainly characterized by a depressed mood and a loss of interest or pleasure, and is additionally characterized by thought or concentration difficulties, an appetite decrease or increase, anxiety, a feeling of worthlessness or guilt, and thoughts related to suicide (suicidal ideation) as well as somatic symptoms including sleep disturbances and fatigability.[1][2] With advances of basic research and clinical studies, the etiology and pathology of depression have been gradually revealed, but not fully elucidated so far.

Depression is a common disease worldwide, with the estimated lifetime prevalence above 10%. The onset age is estimated to be from 20 to 50 years old in half of patients; however, the onset in children and the elderly has been also reported.[3] In the U.S., the prevalence of depression in aged 18 to 29 years is approximately 3-fold higher than that in more than 60 years, and, after early adolescence, the prevalence in women is 1.5 to 3-fold higher than in men, showing that the prevalence of depression varies widely depending on age and sex.[4]

The course of depression varies from only 1 episode in a lifetime to a lifelong disorder with recurrent episodes, and some patients suffer from long-term depressive symptoms despite treatments. Depression is therefore a significant mental and social burden and economic loss for not only patients but also their family, which treatment is necessary.[3]

The goal of treatment for depression is to improve patients' mental and social quality of life by effectively alleviating the depressive symptoms. Depression is mainly treated with pharmacotherapy and psychotherapy, and these treatments are selected according to the severity and pathological condition.[3] As pharmacotherapy in patients with moderate to severe depression, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) have been widely used. These antidepressants, however, have problems such as patients with inadequate response and adverse effects; therefore, development of an antidepressant with a novel profile can broaden treatment options and optimize treatment for depression.

4.1.1 Clinical Pharmacology

Results of clinical pharmacology studies in Japan and overseas are summarized below.

Lu AA21004 was slowly absorbed after oral administration, and the Tmax was approximately 7 to 11 hours. The absolute bioavailability of Lu AA21004 was approximately 75%. The

pharmacokinetics of Lu AA21004 was linear within the dose range between 2.5 and 60 mg. The plasma concentration of Lu AA21004 reached steady state after approximately 2-week multiple doses, and the accumulation index was 5 to 6 based on AUC following multiple doses of 5 to 20 mg/day. There was no food effect on the pharmacokinetics of Lu AA21004.

Lu AA21004 was extensively metabolized in the liver, primarily through oxidation or glucuronic acid conjugation, and CYP2D6 was shown to be the primary enzyme in metabolism of Lu AA21004 to the major metabolite Lu AA34443. Lu AA34443 was pharmacologically inactive, and the active metabolite Lu AA39835 did not cross the blood-brain barrier, although Lu AA39835 was slightly detected in plasma, suggesting that these metabolites are less likely to contribute to the pharmacological effect of Lu AA21004. In addition, Lu AA21004 and its metabolites did not induce or inhibit CYP isozymes *in vitro*, suggesting that clinical significant drug-drug interactions with Lu AA21004 are less likely to occur.

The T1/2 of Lu AA21004 was approximately 66 hours, and two- thirds of its metabolites were excreted in urine, and one-third were excreted in feces. The excretion of unchanged Lu AA21004 was slightly noted in feces.

After multiple doses of Lu AA21004, 5-HTT occupancy in raphe nuclei was approximately 50% at doses of 5 mg/day, 65% at 10 mg/day, and 80% or more at 20 mg/day.

Based on results of studies in Caucasian and Japanese subjects, there were no statistically significant differences in the pharmacokinetics and 5-HTT occupancy of Lu AA21004 between the races.

4.1.2 Overseas Phase II/III Clinical Studies

A total of 12 overseas placebo-controlled, double-blind, short-term studies (Studies 11492A, 11984A, 303, 304, 305, 13267A, 315, 316, 317, CCT-002, 12541A and 14122A) were conducted to evaluate the efficacy of Lu AA21004 for the treatment of MDD. Study CCT-002 was a multinational study including Japan.

The changes from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score were analyzed by mixed model repeated measures (MMRM) in the individual studies; and the results of the 11 of 12 studies mentioned above except for Study 12541A for elderly patients were used for meta-analysis. As for the mean changes from baseline in the MADRS total score at Week 6 or 8, the differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were -2.3 ($p = 0.007$), -3.6 ($p < 0.001$) and -4.6 ($p < 0.001$), respectively, and all of them were statistically significant. In addition, although the mean difference between the 15 mg group and placebo group was -2.6, not statistically significant. MADRS response rate (MADRS response is defined as a $\geq$ 50% decrease from baseline in the MADRS total score) in the subjects treated with Lu AA21004 was 46% to 49%, whereas that in the subjects treated with placebo was 34% ($p < 0.01$). These results suggested Lu AA21004 at doses of 5 to 20 mg/day was effective.

For comprehensive safety evaluation including the above-mentioned short-term studies and long-term studies (Studies 11492C, 11984B, 301, 13267B and 314), treatment with Lu AA21004 at doses of 5 to 20 mg/day was safe and well tolerated. The most common TEAE in the

Lu AA21004 groups was nausea, and gastrointestinal TEAEs were occurred more frequently in female than male. Most TEAEs were mild or moderate and occurred within the first 2 weeks of treatment. In addition, TEAEs were usually transient, and did not generally lead to discontinuation of the study medication.

Abrupt discontinuation of antidepressants may result in discontinuation symptoms, however, there were no clinically relevant differences in the incidence or nature of discontinuation symptoms between the Lu AA21004 groups and placebo group.

The incidence of self-report sexual dysfunction in the Lu AA21004 groups was low, and was similar to that in the placebo group. In the study using a rating scale (Arizona Sexual Experience Scale) for sexual dysfunction, the incidence of sexual dysfunction at doses of 5 to 15 mg/day of Lu AA21004 was similar to that of placebo, but that at 20 mg/day was higher than placebo.

Lu AA21004 had no clinically significant effect on weight, heart rate, blood pressure, and hepatic and renal functions. Moreover, Lu AA21004 also had no clinically significant effect on ECG parameters (QT interval, QTc interval, PR interval and QRS interval). In a thorough QTc study in healthy adult subjects, Lu AA21004 at doses up to 40 mg/day had no potential for prolongation of QT/QTc intervals.

4.1.3 Japanese Phase II/III Clinical Studies

In Japan, 2 placebo-controlled, short-term studies (Study CCT-002 [multinational study] and Study CCT-003 [Japan local study]) were conducted in subjects with MDD. In addition, a long-term extension study (Study OCT-001) was conducted in those who completed Study CCT-003.

Study CCT-002 was conducted in 14 countries including Japan, Europe and the Asia Pacific region to evaluate the efficacy and safety of Lu AA21004 at doses of 5, 10 and 20 mg/day. For the mean changes from baseline in the MADRS total score at Week 8 (last observation carried forward [LOCF]) in the primary efficacy analysis (analysis of covariance [ANCOVA]), the mean differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were -0.61 ($p = 0.91$), -1.69 ($p = 0.30$) and -1.82 ($p = 0.24$), respectively. In addition, in the same analysis for Japanese population, the mean differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were 0.89, -2.74 and -3.45, respectively.

In Study CCT-002, Most TEAEs were mild or moderate, and TEAEs reported in more than 5% of subjects in any Lu AA21004 groups were nausea, nasopharyngitis, headache, dizziness, constipation, dry mouth, and insomnia. Of these, TEAEs with higher ($\geq$ 2-fold) incidence in any Lu AA21004 groups than that in placebo group were nausea, constipation, dry mouth, dizziness and insomnia.

In Study CCT-003, the efficacy and safety of Lu AA21004 at doses of 5 and 10 mg/day were evaluated in Japanese subjects with MDD. For the mean changes from baseline in the MADRS total score at Week 8 (LOCF) in the primary efficacy analysis (ANCOVA), the mean differences of the Lu AA21004 5 and 10 mg group compared to the placebo group were -2.03 ($p = 0.10$) and -1.04 ($p = 0.40$), respectively.

In Study CCT-003, TEAEs reported in more than 5% of subjects in any Lu AA21004 groups were nausea, diarrhoea, nasopharyngitis, somnolence, headache, and suicidal ideation. Of these, TEAEs with higher (≥2-fold) incidence in the Lu AA21004 groups than that in the placebo group were nausea and suicidal ideation. For suicidal ideation, the incidence in the 10 mg group (8 subjects; 6.6%) was higher than in the placebo group (2 subjects; 1.6%) and 5 mg group (1 subject; 0.8%). In general, most TEAEs were mild or moderate, suggesting that there were no significant safety concerns about Lu AA21004.

In the open-label long-term extension study (Study OCT-001), the safety of 52 week treatment of Lu AA21004 at flexible doses of 5 to 20 mg/day was evaluated in subjects who completed Study CCT-003. In Study OCT-001, TEAEs reported in more than 5% of subjects were nasopharyngitis, nausea, seasonal allergy, headache, weight increased, diarrhoea, vomiting, alanine aminotransferase (ALT) increased, somnolence, malaise, influenza, and blood creatine phosphokinase increased. No long-term specific TEAEs were observed, and most TEAEs were mild or moderate, suggesting that there were no significant safety concerns in a long-term treatment of Lu AA21004.

4.2 Rationale for the Proposed Study

In Europe and the U.S., the efficacy and safety of Lu AA21004 were demonstrated at doses of 5 to 20 mg/day and Lu AA21004 has already been approved for marketing. For 2 short-term studies (Studies CCT-002 and CCT-003) including Japanese MDD patients, there are no statistically significant differences in the efficacy between any Lu AA21004 groups and the placebo group; however, in Study CCT-002, changes from baseline in the MADRS total score in the 10 and 20 mg groups were grater than in the placebo group in both overall population and Japanese population, and these results appeared to be supported by the result of 10 mg group in Study CCT-003.

Based on these results, if a statistically significant difference between the Lu AA21004 10 or 20 mg group and the placebo group is shown in the planned study (Study CCT-004), it is considered that the hypothesis of the efficacy of Lu AA21004 at doses of 10 and 20 mg in the Japanese population in Study CCT-002 can be verified.

The results of Studies CCT-002, CCT-003 and OCT-001 suggested that there were no significant safety concerns about Lu AA21004 at the dose up to 20 mg, but further data collection may provide more appropriate safety evaluation.

From the above, this study is designed as an additional phase III study to evaluate the efficacy and safety of Lu AA21004 in Japanese patients with MDD.

Pharmacogenomic analyses may be conducted to evaluate a possible contribution of genetic polymorphism on drug response affecting the efficacy and safety of Lu AA21004. Participation of subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research with banked samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the efficacy of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.

5.1.2 Secondary Objectives

- To evaluate the safety and tolerability of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.
- To evaluate the efficacy of Lu AA21004 (10 or 20 mg/day) on cognitive functions after 8 weeks of treatment in Japanese patients with MDD.

5.1.3 Additional Objectives

- To analyze the plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 using population pharmacokinetic analyses.

5.2 Endpoints

5.2.1 Efficacy Endpoints

5.2.1.1 Primary Endpoint

- Change from baseline (i.e. at the start of the double-blind treatment period) in the MADRS total score after 8 weeks of treatment.

5.2.1.2 Secondary Endpoints

- MADRS response after 8 weeks of treatment (LOCF).
  (MADRS response is defined as a ≥50% decrease in the MADRS total score from baseline).
- MADRS remission after 8 weeks of treatment (LOCF).
  (MADRS remission is defined as the MADRS total score of ≤10).
- Change from baseline in the Hamilton Depression Rating Scale (HAM-D17) total score after 8 weeks of treatment (LOCF).
- Clinical global impression scale-Improvement (CGI-I) score after 8 weeks of treatment (LOCF).
- Change from baseline in the clinical global impression scale-Severity (CGI-S) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Sheehan Disability Scale (SDS) score after 8 weeks of treatment (LOCF).

- Change from baseline in the Digit Symbol Substitution Test (DSST) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Perceived Deficits Questionnaire (PDQ-5) score after 8 weeks of treatment (LOCF).

5.2.2 Pharmacokinetic Endpoint

- Plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835.

5.2.3 Safety Endpoints

- Adverse events
- Weight
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

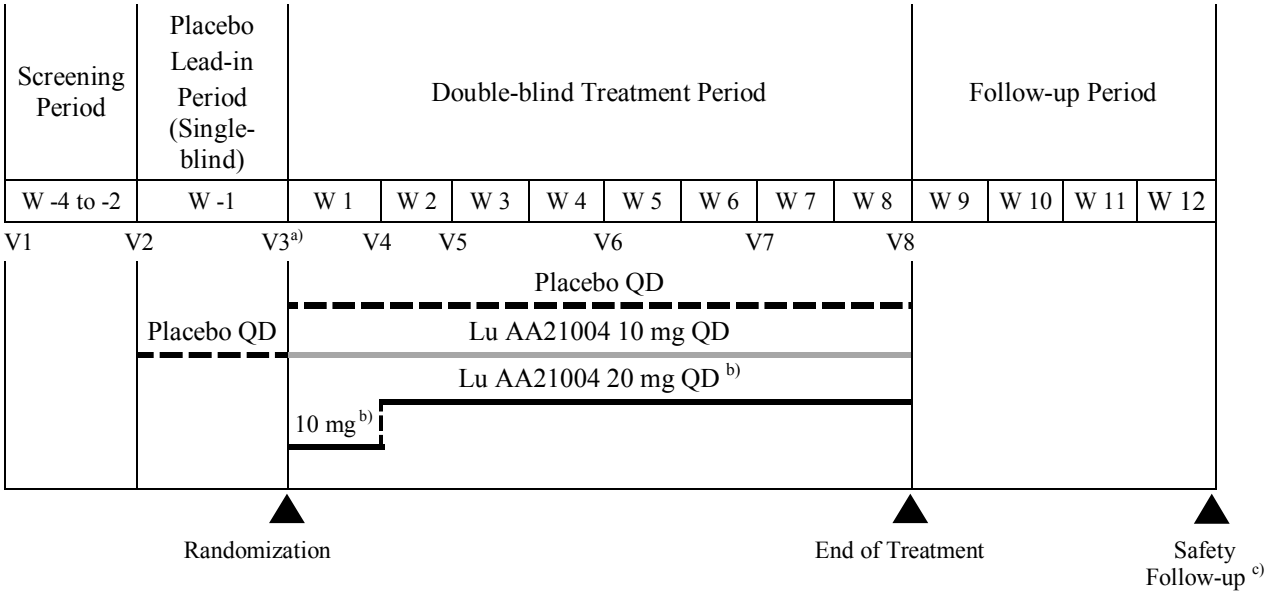
This is a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the efficacy and safety of 8-week treatment of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) in Japanese subjects with MDD.

This study consists of a 1-to 3-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week safety follow-up period. Subjects who fulfill all inclusion criteria and none of exclusion criteria at the start of screening period (Visit 1) and at the start of placebo lead-in period (Visit 2) will move into the placebo lead-in period and receive placebo once daily for 1 week in a single-blind manner. Afterwards, these who fulfill all the inclusion criteria and none of the exclusion criteria at the start of double-blind treatment period (Visit 3) will move into the double-blind treatment period and will be randomized in a 1:1:1 ratio to one of the following treatment groups: the placebo group, the Lu AA21004 10 mg/day group or the Lu AA21004 20 mg/day group. Subjects in the placebo group and the Lu AA21004 10 mg/day group will receive placebo and Lu AA21004 10 mg, respectively, once daily from the day after Visit 3 for 8 weeks in a double-blind manner. Subjects in the Lu AA21004 20 mg/day group will receive Lu AA21004 10 mg once daily from the day after Visit 3 for 1 week and thereafter Lu AA21004 20 mg once daily for 7 weeks in a double-blind manner. Subjects in any treatment groups will visit study sites at Week 1, 2, 4, 6 and 8 during the double-blind treatment period for examinations/observations/assessments.

A safety follow-up contact (visit or phone call) will be made 4 weeks after the completion of the double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or the double-blind treatment period will be requested to visit the study site for the end-of study assessments within 7 days after the discontinuation decision is made wherever possible, and will be contacted 4 weeks after the last dose of the study medication for safety follow-up.

A schematic of the study design is shown in Figure 6.a.

A schedule of examinations/observations/assessments is listed in Appendix A.



W: week, V: visit, QD: once daily
a) Subjects will be randomized on the day of visit at the start of double-blind treatment period (Day -1). Subjects will start the double-blind treatment from the next day (Day 1).
b) Subjects will receive 10 mg/day for the first 1 week, and then increase the dose to 20 mg/day from the 2nd week.
c) Safety follow-up assessment will be conducted by visit to the site or on telephone.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Subject Population

It has been reported that the placebo response rate in subjects with single major depressive episode is higher than that in subjects with recurrent major depressive episode.[5] Since it is important to exclude subjects with high placebo response from clinical studies of antidepressants, subjects with recurrent major depressive episode are eligible for this study. In order to adequately evaluate the efficacy and safety, subjects with moderate to severe MDD are eligible for this study, and subjects with mental disorder other than MDD are excluded from this study.

6.2.2 Study Design

This study is designed based on Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of PFSB/ELD dated 16 November 2010).[3]

A double-blind, randomized, placebo-controlled study is designed for adequate evaluation of the drug efficacy and safety and is used as a standard study design for antidepressants. The use of placebo has continued to be a subject of discussion on the grounds of possible worsening of depressive symptoms or potential increase in suicidal risk; however, there is no evidence that assignment to placebo results in permanent harm or an increased risk of committing suicide.

Subjects at significant risk of suicide are ineligible for this study. Furthermore, suicidal risk of a subject will be assessed using C-SSRS at every visit.

The subjects will be informed about the possibility of receiving placebo, the possible risks with placebo, and their right to withdraw from the study at any time. To a subject who discontinues the study, any other appropriate treatment will be provided based on the investigator's decision.

In addition, a 1-week placebo lead-in period is set prior to the double-blind treatment period to exclude subjects who highly respond to placebo from the study, and thereby subjects who have significantly improvement or aggravation of depressive symptoms during the placebo lead-in period will be excluded.

Justification for sample size is described in Section 13.3.

6.2.3 Doses

In overseas phases II and III studies, the efficacy of Lu AA21004 at doses of 5, 10 and 20 mg/day was shown, with no significant safety concerns. In addition, based on the results of meta-analyses in 11 placebo-controlled, double-blind, short-term studies, the differences of the mean changes from baseline in the MADRS total score at Week 6 or 8 between the Lu AA21004 5, 10 or 20 mg group and the placebo group were -2.3 ($p = 0.007$), -3.6 ($p < 0.001$), and -4.6 ($p < 0.001$), respectively, showing that the difference with the placebo group became greater with the dose increase of Lu AA21004.

In Study CCT-002 for subjects with MDD including Japanese, Lu AA21004 was safe up to a dose of 20 mg/day. And although no statistically significant differences had been demonstrated in the efficacy between the Lu AA21004 groups and the placebo group, the efficacy of Lu AA21004 in the 10 and 20 mg groups was grater than in the placebo group in both overall population and Japanese population.

From the results of previous Japanese and overseas studies above, since there were no significant safety concerns about Lu AA21004 up to a dose of 20 mg/day and Lu AA21004 at doses of 10 and 20 mg/day is expected to be effective, these 2 doses will be assessed in this study.

6.2.4 Endpoints

MADRS or HAM-D is recommended for efficacy assessments in Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of PFSB/ELD dated 16 November 2010).[3] Based on the guideline, the MADRS, which is designed to be sensitive to the changes in severity of core symptom of depression, will be used for the primary endpoint evaluation [6], and the HAM-D for the secondary endpoint evaluation in this study.[7] CGI-S and CGI-I will be used to assess subject's overall severity and improvement of depression.[8] In addition to these objective assessments of symptoms, SDS will be used in this study to assess patient's subjective treatment effects on social function disabilities due to depression.[9]

Results of overseas studies of Lu AA21004 showed that Lu AA21004 improved cognitive functions in subjects with MDD. In this study, DSST and PDQ-5 will be used to explore the effect of Lu AA21004 on cognitive functions in Japanese subjects with MDD.

Safety and tolerability of Lu AA21004 will be evaluated by monitoring of AEs, vital signs, weight, clinical laboratory tests, ECGs, and physical examinations. In addition with these safety evaluations, since it is important to assess suicidal risk for clinical evaluation of antidepressants, suicidal risk will be assessed using C-SSRS at each visit in this study.[10][11]

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject suffer from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x).
4. The subject is a man or a woman aged 20 to 75 years (both inclusive) at the time of informed consent.
5. The reported duration of the current major depressive episode is 3 to 12 months (both inclusive) at the start of screening period.
6. The subject has a MADRS total score ≥26, a HAM-D17 total score ≥18, and a CGI-S score ≥4 at the start of screening period, the start of placebo lead-in period and the start of double-blind treatment period.
7. A female subject of childbearing potential* who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent to the end of the follow-up period.

* Definitions of a female subject of childbearing potential are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities of pregnancy are defined in Section 9.1.14 Pregnancy.

<Justification for Inclusion Criteria>

Criteria 1 and 2 were set as standard requirements to conduct clinical studies.

Criterion 3 was set to identify the target disease and diagnostic criteria for this study. In addition, in order to reduce the possibility of enrolling subjects who highly respond to placebo, the primary diagnosis was set as recurrent MDD.

Criterion 4 was set for the lower limit of age as 20 years old because it was the adult age under the Civil Code. In addition, since the previous pivotal phase II or III studies set 75 years old as the upper limit of age, the upper limit of age in this study was set as 75 years old in the light of the possible comparison with the previous data.

Criterion 5 was set to enroll subjects who had persistent major depressive episode for at least 3 months in consideration of diagnostic certainty. The upper limit of episode duration was set as 12

months since, in general, subjects with chronic depressive symptoms are highly likely to have other concurrent mental disorder and the low possibility that the depressive symptoms would completely disappear with antidepressant drugs.

Criterion 6 was set to enroll subjects with moderate or more severe MDD in severity as eligible for this study.

Criterion 7 was set with respect to the safety risk related to pregnancy in female subjects.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has any following current or past history of psychiatric disorder and/or neurological disorder:
   - Any current psychiatric disorder other than MDD as defined by DSM-IV-TR (To be assessed by Mini International Neuropsychiatric Interview: MINI). A subject who exhibits symptoms of anxiety is eligible unless the subject fulfills the diagnostic criteria for a current anxiety disorder per DSM-IV-TR.
   - Current diagnosis or history of manic, mixed or hypomanic episode, MDD with psychotic features, schizophrenia or any other psychotic disorder (including substance-related mental disorders, or mental disorders due to a general medical condition) as defined by DSM-IV-TR.
   - Current diagnosis or history of any substance-related disorder (except nicotine and caffeine-related disorders) as defined by DSM-IV-TR.
   - The subject with a positive urine drug screening result at the start of screening period or the start of placebo lead-in period. In case that a subject showed positive test result at the start of screening period because the test was conducted before washout of pretreatment drug, the subject is eligible as long as he/she shows negative result at the start of placebo lead-in period.
   - Presence or history of any clinically significant neurological disorder (including epilepsy).
   - Any neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).
   - Any DSM-IV-TR axis II disorder.
2. The subject has the current or previous major depressive episode which were considered by the investigator to have been resistant to 2 or more adequate antidepressants treatments of at least 6 weeks duration each at sufficient doses.
3. The subject has received any augmentation therapy (e.g. lithium, T3/T4, lamotrigine, sodium valproate, carbamazepine, additional atypical antipsychotic, or concomitant use of other antidepressant, etc.) for the current major depressive episode.

4. In the opinion of the investigator, the subject has experienced significant number of major depressive episodes in the past, and is suspected of disease other than MDD.
5. In the opinion of the investigator, the subject has experienced the first major depressive episode at his/her young age, and is suspected of disease other than MDD.
6. The subject has a MADRS total score at the start of double-blind treatment period that has improved or aggravated by 25% or more from the score at the start of placebo lead-in period.
7. The subject is significantly non-compliant with the study medication in the placebo lead-in period; e.g., not taking the study medication for 6 or more consecutive days.
8. The subject has received electroconvulsive therapy, vagus nerve stimulation, or repetitive transcranial magnetic stimulation therapy within 6 months prior to the screening period, or plans to initiate such therapy during the study.
9. The subject is receiving cognitive-behavioral therapy or psychotherapy at the time of informed consent, or plans to initiate such therapy during the study.
10. The subject is at significant risk of suicide or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS at the start of screening period, the start of placebo lead-in period or the start of double-blind treatment period, or has attempted suicide within 6 months prior to the start of screening period.
11. The subject has experienced any environmental change (e.g. temporary retirement, returnment, change of residence) considered by the investigator to have the potential to impact on the efficacy evaluation, or plans such environmental changes during the study.
12. The subject is currently receiving drug therapy for thyroid dysfunction.
13. The subject is currently receiving hormonal therapy for gynecological disease.
14. The subject has taken excluded medications during the protocol-specified period, or will require to take excluded medications during the study.
15. The subject has previously received vortioxetine.
16. The subject has received study medication in a previous clinical study of Lu AA21004 (including this study).
17. The subject has a clinically significant chronic liver disease.
18. The subject has a history of severe allergy or hypersensitivity to drugs.
19. The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, neoplastic, skin and subcutaneous tissue disorders, eye disorders, or metabolic disturbance.
20. The subject has clinically significant abnormal vital signs as determined by the investigator at the start of screening period, placebo lead-in period, or double-blind treatment period.

21. The subject has clinically significant abnormal ECG as determined by the investigator, at the start of the screening period, placebo lead-in period, or double-blind treatment period.
22. The subject has clinically significant abnormal findings of clinical laboratory tests as determined by the investigator, or has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN at the start of screening period or placebo lead-in period.
23. If female, the subject is pregnant or lactating.
24. The subject has a disease or takes medications that could, in the opinion of the investigator, interfere with the evaluation of the safety, tolerability, or efficacy.
25. The subject is, in the opinion of the investigator, unsuitable for this study for any other reason.

<Justification for Exclusion Criteria>

Criteria 1, 4, and 5 were set to exclude subjects or the possible subjects with concurrent mental or neurological disorder other than MDD and to adequately evaluate the efficacy and safety for the target disease.

Criterion 2 was set to exclude subjects or the possible subjects with refractory major depression and include adequate subjects for the evaluation of drug effect.

Criterion 3 was set to exclude subjects who have received augmentation therapy and include adequate subjects for the evaluation of drug effect since subjects who are required to receive augmentation therapy may have refractory major depression or concurrent mental or neurological disorder other than MDD.

Criterion 6 was set to exclude subjects who highly respond to placebo and include adequate subjects for the evaluation of drug effect. Subjects who abruptly worsen their symptoms in a short time are also excluded from the study in consideration of the appropriateness of drug effect evaluation and the safety of subjects.

Criterion 7 was set because it influences the evaluation in the placebo lead-in period.

Criteria 8, 9, 11 to 13 were set because they could influence the evaluation of efficacy.

Criteria 10, 17 to 22 were set with respect to the safety of subjects.

Criteria 14 and 24 were set because they could influence the evaluation of efficacy and safety.

Criterion 15 was set because the bias toward Lu AA21004 based on their treatment experience could influence the evaluation of the efficacy and safety.

Criterion 16 was set to avoid duplicated evaluation of subjects.

Criterion 23 was set with respect to the safety risk for pregnant women, fetuses, neonates, or nursing infant.

Criterion 25 was set to exclude subjects who are considered to be unsuitable for this study for any other reason.

7.3 Excluded Medications and Treatments

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Any treatments for depression other than the study medication, including electroconvulsive therapy, vagus nerve stimulation, repetitive transcranial magnetic stimulation, cognitive-behavioral therapy or psychotherapy are prohibited during the study.

A list of prohibited/restricted concomitant medication is provided in Table 7.a.

Table 7.a List of Prohibited or Restricted Concomitant Medications

Drug Class	Comments or Exceptions
84 days before the start of double-blind treatment period (Day -84) through the end of double-blind treatment period (Visit 8) or early termination	
(1) Any investigational drug	
Start of the screening period (Visit 1) through the end of double-blind treatment period (Visit 8) or early termination	
(2) Antidepressants	Including MAOIs.
(3) Anxiolytics (tranquilizers)	Including benzodiazepines.
(4) Hypnotics	Non-benzodiazepines (zolpidem, zopiclone, and eszopiclone) are allowed. However, use of these drugs should be kept to the minimum necessary, and use for 2 or more consecutive days and use at the night before a study visit are NOT allowed. In addition, the type and dose of non-benzodiazepines should NOT be changed from the start of placebo lead-in period (Visit 2) to the end of double-blind treatment period (Visit 8) or early termination.
(5) Antipsychotics	Depot antipsychotics are prohibited within 6 months prior to the start of double-blind treatment period.
(6) Mood stabilizers	Including lithium, valproate, valpromide.
(7) Psychoactive herbal remedies/supplements	Including St. Johns Wort, kava kava, valerian, ginkgo biloba.
(8) Psychotropic agents not otherwise specified	Including tryptophan, melatonin, and dopamine agonists.
(9) Analeptics	
(10) Anti-ADHD	
(11) Anti-Alzheimer's disease	
(12) Anticonvulsants	
(13) Anti-Parkinson’s disease	
(14) Erectile dysfunction drugs	
(15) Anorexics	
(16) Antimigraines	
(17) Antiemetics/antinauseants	Including dopamine antagonists. Only phosphoric acid preparations, bismuth and cola syrup are allowed.
(18) Interferon	
(19) Systemic steroids	Oral preparation and injection are NOT allowed.

(20) Antibiotics	Rifampicin (oral preparation and injection) is NOT allowed.
Start of the placebo lead-in period (Visit 2) through the end of double-blind treatment period (Visit 8) or early termination	
(21) Antiarrhythmics of class Ia, Ic	
(22) Antiulcer drugs	Omeprazole, cimetidine, and sulpiride are NOT allowed.
(23) Anticoagulants/antiplatelet treatment	Including low dose of aspirin as antiplatelet treatment. Low-molecular weight heparins are allowed as needed.
(24) Antidiarrheal agents	Loperamide, bismuth, and kaolin preparations are allowed.
(25) Antihistamines	Loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine are allowed.
(26) Antineoplastics	
(27) Hormones	Chronic use for contraception or treatment of benign prostatic hyperplasia are allowed.
(28) Hypoglycemic agents	Chronic use is allowed.
(29) Insulin	Chronic use is allowed without major change of dose or administration.
(30) Calcium antagonist	Chronic use is allowed without major change of dose or administration.
(31) Narcotic analgesics	Topical administration including for dental use is allowed.
(32) NSAIDs	Episodic use is allowed. Selective COX-2 inhibitors, acetaminophen, and topical NSAIDs are allowed.
(33) Cough/cold agents	Episodic use is allowed. However, chronic use of preparations containing ephedrine, pseudoephedrine, and codeine are NOT allowed for more than 1-week treatment.

MAOI = monoamine oxidase inhibitor, ADHD = attention deficit hyperactivity disorder,
NSAIDs = nonsteroidal anti-inflammatory drugs, COX-2 = cyclooxygenase-2

<Justification for Prohibited or Restricted Concomitant Medications>

(1) was set since other investigational drug could influence the evaluation of the efficacy and safety.

(2) was set since antidepressants could influence the evaluation of the efficacy. Especially, concomitant use of monoamine oxidase inhibitors (MAOIs) was prohibited because concomitant use of MAOIs could enhance serotonin action and influence the evaluation of the efficacy, and because the safety of subjects should be ensured.

(3) was set since anxiolytics (tranquilizers) could improve anxiety which was known to an accompanying symptom of depression and influence the evaluation of the efficacy.

(4) was set since hypnotics could improve insomnia which was known to an accompanying symptom of depression and influence the evaluation of the efficacy. Concomitant use of non-benzodiazepines was allowed as needed because the extent of anxiolytic and carry-over effects of non-benzodiazepines was relatively weak, and thus these effects had only a small influence on efficacy evaluation.

(5) to (13) were set since these drugs had psychotropic activity or central nervous effects and

could influence the evaluation of the efficacy.

(14) was set since erectile dysfunction drugs could improve sexual dysfunction and could influence the evaluation of the efficacy and safety.

(15) was set since anorexics influence the appetite assessment related to depression.

(16) and (17) were set since antimigraines and antiemetics/antinauseants could act on serotonin receptors and influence the evaluation of the efficacy and safety. Especially, concomitant use of antiemetics/antinauseants was prohibited because adverse events associated with the study medication should be appropriately evaluated.

(18) and (19) were set since interferon and systemic steroids could induce depressive symptoms and influence the evaluation of the efficacy.

(20) was set since antibiotics could decrease the plasma drug concentration by inducing drug metabolic enzymes and influence the evaluation of the efficacy and safety.

(21) and (22) were set since antiarrhythmics of class Ia, Ic, and antiulcer drugs could increase the plasma drug concentration by inhibiting drug metabolic enzymes and influence the evaluation of the efficacy and safety

(23) was set since concomitant use of anticoagulants/antiplatelet treatment drugs could enhance bleeding tendency.

(24) was set since gastrointestinal adverse events associated with the study medication should be appropriately evaluated.

(25) was set since drowsiness, an adverse drug reaction of antihistamines, could attenuate insomnia, which was known to an accompanying symptom of depression and influence the evaluation of the efficacy. Concomitant use of only loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine, which are considered to cause less drowsiness, was allowed.

(26) was set since antineoplastics could influence the evaluation of the efficacy and safety.

(27) and (28) were set since hormones and hypoglycemic agents could influence the evaluation of the efficacy and safety. However, chronic use of these drugs at a certain dose was allowed as having little influence on the evaluation.

(29) and (30) were set since insulin and calcium antagonists could induce depressive symptoms. However, chronic use of insulin or calcium antagonist at a certain dose was allowed as having little influence on the efficacy evaluation.

(31) was set since analgesic action of narcotic analgesics could influence the evaluation of the efficacy. However, topical administration such as for dental use is allowed since narcotic analgesics have only a small influence on the evaluation.

(32) was set since the concomitant use of NSAIDs could cause upper gastrointestinal bleeding. However, the episodic use of NSAIDs as well as the concomitant use of selective COX-2 inhibitors, acetaminophen, and topical NSAIDs was allowed since these treatments had a

relatively lower effect on gastrointestinal adverse events.

(33) was set since some cough/cold agents increase the serotonin concentration of the central nervous system. Concomitant use of ephedrine and codeine for more than 1 week was not allowed due to their addictiveness.

7.4 Diet, Fluid, and Activity Control

The investigator or study collaborator should instruct subjects on the following items:

1. The subject must be punctual for visit, undergo physical examination and predefined examinations. If the subject cannot visit, he/she should inform the investigator or study collaborator as soon as possible.
2. If the subject experiences a worsening of conditions on any day the site visit is not scheduled, he/she should inform the investigator or study collaborator of the worsening by telephone or other manners as soon as possible and seek instructions.
3. The subject must take the study medication as instructed by the investigator. If the subject is noncompliant with study treatment, he/she should inform the investigator or study collaborator of the noncompliance with treatment at visit. The subject must return unused study medication and study medication sheets at visit.
4. The subject must not take any medications including over-the-counter products other than medications as instructed by the investigator without advance consulting (except for emergency).
5. If the subject consults other medical institution from the time of informed consent to the end of the follow-up period, notify the physician of medical institution of the subject's participation in this study.
6. If the subject consults other medical institution from the time of informed consent to the end of the follow-up period, notify the investigator of the circumstances and therapy.
7. The subject must visit the site under fasted conditions at Visits 2, 3 and 8 or Early Termination Visit. For visits serum chemistry test is scheduled, the subject visits the site under fasted conditions wherever possible.
8. Female subject of childbearing potential who is sexually active with a nonsterilized male partner must routinely use adequate contraception from the time of informed consent to the end of the follow-up period.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the case report form (eCRF) using the following categories. For the subject who prematurely discontinues the study before entry into the placebo lead-in period or randomization, refer to Section 9.1.18 or 9.1.20, respectively.

1. **Pretreatment event (PTE) or adverse event (AE)**
   The subject has experienced a pretreatment event (PTE) or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. **Liver function test (LFT) abnormalities**
   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study medication treatment:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
   - ALT or AST >5 × ULN and persists for more than 2 weeks, or
   - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. **Significant protocol deviation**
   The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. **Lost to follow-up**
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. **Voluntary withdrawal**
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. (i.e., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category.)
6. **Study termination**
   The sponsor, IRB, or regulatory agency terminates the study.
7. **Pregnancy**
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.

8. **Lack of efficacy**
   The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
9. **Medication noncompliance**
   The subject did not take the study medication for 6 or more consecutive days.
10. **Other**
    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5.1 Additional Guidance for Withdrawal Criteria

Any signs of suicidal risk will be assessed throughout the study by C-SSRS and MADRS assessments and clinical judgment of the investigator. If the subject has a significant risk of suicide in the opinion of the investigator, or the subject has the MADRS score of ≥5 on item 10 (suicidal thoughts), the subject will prematurely discontinue the study.

If subject's underlying diseases become exacerbated, and the investigator concludes any excluded medications or treatment is required, the subject will prematurely discontinue the study.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

Table 8.a Study Medication

Name	Active Substance	Dosage Form	Strength	Manufacture
Lu AA21004 tablet	1-[2-(2,4-dimethyl-phenyl sulfanyl)-phenyl]-piperazine, hydrobromide	Indistinguishable round biconvex tablets	10 mg or 20 mg	Takeda Pharmaceutical Company Limited
Placebo tablet	None		–	

The study medications are identical in appearance.

As for the study medications for the placebo lead-in period, 14 tablets of placebo are packaged in 1 press-through pack (PTP) sheet, and a single sheet is enclosed in an outer carton. The 1 outer carton (including 7 days' spare tablets) will be provided to each subject in the placebo lead-in period.

As for the study medications for the double-blind treatment period, 14 tablets of Lu AA21004 or placebo are packaged in 1 PTP sheet. For Week 1 in the double-blind treatment period, 1 sheet (including 7 days' spare tablets) is enclosed in an Inner Carton 1, and, for Weeks 2 to 8 in the double-blind treatment period, 5 sheets (including 21 days' spare tablets) are enclosed in an Inner Carton 2. Inner Cartons 1 and 2 are packed together in an outer carton. The 1 outer carton will be provided to each subject in the double-blind treatment period.

The outer carton is labeled with a note that the formulation therein is used for a clinical study and pertinent information of the name and quantity of the study medication, the sponsor's name and address, manufacturing number, and storage conditions.

8.1.2 Storage

The study medications should be stored at room temperature (1°C to 30°C).

The study medication must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. The study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

For the placebo lead-in period, administration of the study medication will be started on the day after Visit 2, and subjects will orally take 1 tablet of placebo once daily.

For the double-blind treatment period, administration of the study medication will be started on the day after Visit 3, and subjects will orally take 1 tablet of Lu AA21004 at a dose of 10 mg or 20 mg or placebo once daily.

The investigator or designee should instruct subjects to take the study medication at the same time, a certain time in the morning to the extent possible, throughout the study. The study medication can be taken under both fed and fasted conditions.

At each visit, subjects will be provided with necessary and sufficient amount of the study medications to be used by next visit by the investigator or designee. The investigator or designee must instruct subjects to bring the all remaining study medication and container (PTP sheets) at each visit.

The dose (tablet count) that will be provided to each group and regimen are shown in Table 8.b.

Table 8.b Dose and Regimen

Treatment Group	Regimen	Tablet Count/Dose		
		Placebo Lead-in Period	Double-blind Treatment Period (Week 1)	Double-blind Treatment Period (Weeks 2 to 8)
Placebo Group	Oral, once daily	Placebo tablet ×1	Placebo tablet ×1	Placebo tablet ×1
Lu AA21004 10 mg/day Group	Oral, once daily	Placebo tablet ×1	Lu AA21004 10 mg tablet ×1	Lu AA21004 10 mg tablet × 1
Lu AA21004 20 mg/day Group	Oral, once daily	Placebo tablet ×1	Lu AA21004 10 mg tablet ×1	Lu AA21004 20 mg tablet ×1

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of the study medication to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. This includes any concomitant medication received at a dose greater than that prescribed to the subject.

All cases of overdose will be documented as AEs on an AE page of the eCRF according to Section 10.2.1, and should be reported as a special interest AE according to Section 10.2.1.3 (with or without associated AEs). Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure in Section 10.2.2.

In the event of an overdose of the study medication, the investigator should take general symptomatic and supportive treatment, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration,

pulse, blood pressure, and other appropriate signs should be monitored and general supportive treatment should be conducted.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive the next available medication ID number allocated to each study site. The Medication ID Number will be entered onto the eCRF.

8.3 Randomization Code Creation and Storage

Randomization personnel (a person designated by the sponsor) will generate the randomization code. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The emergency key code administration center will maintain the emergency key code until its breaking for an emergency or completion of database lock of all subjects.

Since analytical results of the plasma concentration may jeopardize maintenance of study blinding, the analytical laboratory will keep the final analytical results and not disclose to a third party until unblinding of the study. The analytical laboratory will report the results to the sponsor after they receive the notification of unblinding of the study. However, the analytical laboratory may disclose the results to the sponsor through a responsible person for randomization before unblinding of the study taking measures to secure the blinding such as reassignment of the medication number so that persons in the laboratory may not identify a subject. The detailed procedure will be specified in the separately created manual for handling of biological specimen for pharmacokinetic analysis.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject.

For unblinding, the investigator may contact the emergency key code administration center and obtain allocation information of the study medication.

The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking, and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

For details of unblinding procedure, refer to the manual for Breaking of Emergency Key Code.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage, and management of study drug created by the sponsor, according to which the site designee will appropriately manage the

sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

A separate informed consent form pertaining to pharmacogenomic research must be obtained prior to collecting a sample for Pharmacogenomic Research for this study (see Section 9.1.16). The provision of consent to research in pharmacogenomics is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, alcohol use, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any mental disorders other than MDD (including dysthymic disorder, generalized anxiety disorder, obsessive-compulsive disorder, as defined by DSM-IV-TR) that resolved within 1 year prior to signing of informed consent. Medical history of MDD (past major depressive episode) to be obtained will include determining whether the subject had MDD according to Section 9.1.4.2.

Medication history information to be obtained includes any medication that stopped prior to signing of informed consent and used for treatment of the current major depressive episode or accompanying symptoms. Name of medication used, dose level, unit, dose frequency, route of administration, and the dates of the initial dose and the last dose must be recorded.

9.1.3 Diagnosis of MDD

Diagnosis of MDD and other psychiatric disorders must be based on DSM-IV-TR criteria. In addition, the Mini International Neuropsychiatric Interview (MINI) must be used as an auxiliary diagnostic tool. MINI is a structured diagnostic interview designed to provide a brief standardized evaluation of major Axis I psychiatric disorders in DSM-IV-TR. The investigator can use the MINI after a training session for diagnosis of MDD. Only the version provided by the sponsor that has been validated in Japanese will be used in this study.

9.1.4 Assessments of Major Depressive Episode

9.1.4.1 Current Major Depressive Episode

The following items will be assessed for the current major depressive episode.

- Start date
- Symptom (Select from 9 symptoms listed below as defined by DSM-IV-TR.)
- Psychotherapy (yes or no)

<Symptoms of Major Depressive Episode>

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of weight in a month), or decrease or increase in appetite nearly every day.

(4) Insomnia or hypersomnia nearly every day.

(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

(6) Fatigue or loss of energy nearly every day.

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

9.1.4.2 Past Major Depressive Episode

The following items will be assessed for past major depressive episode.

- Start date and duration of each past major depressive episode.
- Antidepressant drug treatment for each past major depressive episode (yes or no). If the subject has received an antidepressant drug, category of the drug (select from SSRIs, SNRIs, or other antidepressant drugs.) and duration will be recorded.

9.1.5 Physical Examination Procedure

A physical examination will consist of the following body systems:

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

All subsequent physical examinations should assess clinically significant changes from the examinations prior to first dose.

9.1.6 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height will be collected in centimeters without decimal places, and weight will be collected in kilograms (kg) to 1 decimal place. The BMI will be calculated by the sponsor to 1 decimal place with the formula provided below:

$$\text{Metric: BMI} = \text{weight (kg)}/\text{height (m)}^2$$

9.1.7 Vital Sign Procedure

Vital signs will include body temperature (infra-axillary measurement), sitting blood pressure (resting more than 5 minutes), and pulse (bpm).

9.1.8 Efficacy Evaluation

The efficacy will be evaluated using rating scales (MADRS, HAM-D, CGI-S/I, SDS, DSST, and PDQ-5). These assessments should be performed by the investigator who has sufficient experience in clinical practice of diagnosing and treating MDD and who was approved by the sponsor as a rater in this study. The same rater should, whenever possible, assess the same subject throughout the study.

In principle, the MADRS should be performed first at visits that the above-mentioned multiple rating scales will be performed. Efficacy data using these rating scales should be recorded in eCRF by the next visit of the subject at the latest.

In addition, self-report of depressive symptoms by subjects will be performed using Quick Inventory of Depressive Symptomatology (QIDS-J). For QIDS-J, any sequencing order with other rating scales is allowed. QIDS-J data will not be recorded in the eCRF.

9.1.8.1 Rating and Rating Training for MDD

Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS will be used for a primary efficacy measurement. The MADRS is a depression rating scale consisting of 10 items representing the core symptoms of depression.[6] The MADRS is rated using Structured Interview Guide for MADRS (SIGMA). The rating should be based on a clinical interview with the subject, moving from broadly phrased questions about symptoms to more detailed questions. The rating is performed based on the most severe

condition of the subject during the past 1 week, and each item is rated from 0 to 6. Item 1 and Items 3 to 10 are based on subject report, and Item 2 is based on the observation of the subjects. The rater must decide whether the rating for each item lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). Each item score and the total score of all items should be recorded on the eCRF.

Before the first rating, the investigators (hereinafter referred to as [potential] raters in this section) will attend a MADRS training session. Potential raters will watch and score a recorded MADRS interview (video/DVD). A discussion will follow the training session to achieve alignment among raters on the scoring of each individual item.

The sponsor will qualify the raters who achieve the scoring in the training session, and issue a certificate. No subject may be rated before the rater receives the certificate. For potential raters who cannot attend the training session or who are not qualified in the training session, similar MADRS training will be held in each study sites.

If a rater is changed or added during the course of the study, the newly appointed rater must complete all training requirements satisfactorily and must be approved by the sponsor.

Hamilton Depression Rating Scale (HAM-D)

The HAM-D is a depression rating scale that assesses overall symptoms of depression including somatic symptoms. The rater must rate each item score between 0 to 2/3/4 based on a clinical interview with the subject.[7] The rating should be based on patient's condition during the past 1 week prior to the time of assessment. The HAM-D21 is used for rating, and total score of the first 17 items is used as HAM-D17 total score. Each item score and the HAM-D17 total score should be recorded on the eCRF. Prior to the first rating, potential raters will attend a session on concerns to be addressed for the rating of HAM-D.

Clinical Global Impression Scale (CGI)

The CGI consists of 2 sub-scales: CGI-S and CGI-I.[8] The CGI-S assesses the physician's impression of the subject's current mental disorder state. The rater should use his/her total clinical experience with this subject population and rate the current severity of the subject's mental disorder on a 7-point scale. The CGI-I assesses the subject's improvement (or worsening). The rater is required to assess the subject's condition relative to baseline* on a 7-point scale. In all cases, the assessment should be made independent of whether the rater believes the improvement is study medication-related or not. Each score of CGI-S and CGI-I should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the rating of CGI.

* The start day of the double-blind treatment period (Visit 3) is defined as baseline. However, for the assessment at the start of double-blind treatment period (Visit 3) or early termination visit prior to the start of double-blind treatment period, CGI should be assessed comparing with the score at the start of placebo lead-in period (Visit 2).

9.1.8.2 Social Function Assessment

Sheehan Disability Scale (SDS)

The SDS is a scale that assesses disabilities in 3 social function domains subjectively.[9] The subject self-rates the extent to which his or her work/school, social life/leisure activities, and home life/family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale. The SDS also addresses the number of days the above functions were lost or under-productive due to the symptoms. Each item score should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the rating of SDS.

9.1.8.3 Cognitive Function Assessments

Digit Symbol Substitution Test (DSST)

The DSST is a test battery used for assessment of cognitive functions. In the DSST, subjects are shown 9 digit-symbol pairs and required to pair the same digit and symbol combination. Levels of cognitive functions are assessed by the number of correct symbols (0 to 133 scores) within the time limit. DSST scores should be recorded on the eCRF. At a start of the placebo lead-in period (Visit 2), subjects will complete the sample items prior to the actual test, but the results of the sample items should not be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of DSST.

Perceived Deficits Questionnaire (PDQ-5)

The PDQ-5 is a self-report questionnaire by subjects used for assessment of their cognitive functions. PDQ-5 consists of 5 questions and provides an assessment of several domains of cognitive functions: attention, retrospective memory, prospective memory, and planning and organization. Sub-scores of each item score (0 to 4 scores) and the total score of all items should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of PDQ-5.

9.1.8.4 Self-report Assessment of Depressive Symptoms and Assessment Monitoring

Quick Inventory of Depressive Symptomatology (QIDS-J)

The QIDS-J is a basic self-report depression scale, and the partially revised version provided by the sponsor will be used for this study. Subjects will enter the responses to each questions of the QIDS-J into the terminal. The rater should not see the responses and not record them on the eCRF. The responses will be reviewed by the expert who has adequate experience in assessment of depression. Appropriateness of the efficacy evaluation will be monitored by comparing with results of other efficacy evaluation of the relevant subject.

9.1.9 Suicidal Risk Assessments

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical study. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.[10][11] Responses to each question will be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of C-SSRS.

9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through Visit 8 or Early Termination Visit), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF.

9.1.11 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent, except for accompanying symptoms of MDD. This includes clinically significant laboratory, vital sign, ECG, or physical examination abnormalities noted at the first examination after signing of informed consent in the opinion of the investigator. The condition (i.e., diagnosis) should be described.

9.1.12 Procedures for Clinical Laboratory Samples

The items of clinical laboratory tests are shown in Table 9.a. Samples will be collected and handled in accordance with the separate operation manual. For clinical laboratory tests, the maximum volume of blood at any single visit is approximately 10 mL.

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**	
Red blood cells (RBC)	Albumin	Glucose (fasting or non-fasting) [a)]
White blood cells (WBC)	AST	Total protein
Hemoglobin	ALT	Potassium
Hematocrit	γ-GTP	Sodium
Platelets	Alkaline phosphatase	Calcium
Neutrophils	Total bilirubin	Chloride
Eosinophils	Direct bilirubin	Lipids (fasting or non-fasting) [a)]
Basophils	(Conjugated bilirubin)	Triglycerides
Lymphocytes	Creatinine	Total Cholesterol
Monocytes	Creatine kinase	High-density lipoprotein cholesterol
	Blood urea nitrogen (BUN)	Low-density lipoprotein cholesterol (direct measurement)
	Uric acid	
Hormonal Test (Visit 1 only)	**Urinalysis**	
Thyroid stimulating hormone (TSH) [b)]	Protein (qualitative)	Urine pH
Free T_4 [b)]	Glucose (qualitative)	Microscopic examination [c)] (white blood cells, red blood cells, and casts)
	Occult blood (qualitative)	
Pregnancy test (female subjects of childbearing potential only)		
Urine human chorionic gonadotropin (hCG)		
Urine Drug Screening [d)]		
Amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaines, morphines, phencyclidines, and tricyclic antidepressants		

a) Blood will be collected under fasted conditions at Visits 2, 3 and 8 or Early Termination Visit. For other visits, blood will be collected under fasted conditions wherever possible.
b) TSH will be measured at Visit 1, and when TSH value is outside the normal range, free T_4 will be measured. If a clinically significant abnormality of thyroid gland is found based on the results of TSH and free T_4, the subject will be excluded from the study.
c) Microscopic examination will be performed if abnormality is found in any item in urinalysis.
d) If the subject has a positive urine drug result, he/she will be excluded from the study. However, when the subject has a positive urine test result at Visit 1 because the urine test was performed prior to washout of pretreatment drug, the subject is eligible for the study if he/she has a negative drug test result at Visit 2.

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and hormonal test. The local laboratory will perform the pregnancy test and urine drug screening. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-GTP, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. If the ALT or AST remains elevated >3 × ULN on these 2 consecutive occasions, the abnormality should be recorded as a special interest AE (hepatic impairment) by the investigator, and follow

the procedure specified in Sections 10.1.5.2 and 10.2.1.3. After additional examinations and detailed monitoring, the investigator must contact the sponsor for consideration of possible discontinuation of the study medication, discussion of the relevant subject details and possible alternative etiologies.

If subjects experience ALT or AST >3 × ULN and total bilirubin >2 × ULN, the investigator must refer to instructions in Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject and Section 10.2.3 Reporting of Abnormal Liver Function Tests.

9.1.13 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, to the end of the follow-up period, female subjects of childbearing potential (e.g., non-sterilized or premenopausal female subjects) who are sexually active with a nonsterilized male partner must use adequate contraception. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed, and subjects will receive continued guidance with respect to the avoiding pregnancy as part of the study procedures (Appendix A).

At visits when pregnancy tests are performed, subjects must be confirmed of having a negative urine hCG pregnancy test, as well as at the follow-up examination.

9.1.14 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any study medication should be immediately discontinued.

If the pregnancy occurs during administration of active study medication from the start of the study medication in the double-blind treatment period to the end of the follow-up period, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the attachment.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician (obstetrics and gynecology specialist) that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.15 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: RR interval, PR interval, QT interval, QRS interval, and QTcB interval. QTcF interval will be calculated by the sponsor. ECG traces recorded on thermal paper should be photocopied to avoid degradation of trace over time.

9.1.16 Pharmacogenomic Sample Collection

One 5-mL whole blood sample for pharmacogenomics will be collected at the start of placebo lead-in period (Visit 2) or at the earliest possible time during the study from subjects who signed informed consent of pharmacogenomics and entered into the placebo lead-in period for possible exploratory investigation of markers enabling the prediction of drug response.

Pharmacogenomic sample should not be collected from any subject who has received comparable bone marrow transplant or whole blood transfusion within 6 months of any sample collection.

See the separately created procedure for collecting, handling, and storage of pharmacogenomic samples.

9.1.17 Pharmacokinetic Sample Collection and Analysis

9.1.17.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples will be collected in concurrence with blood collection for clinical laboratory tests. The exact date and time of the blood collection and dosing times of the last 2 doses prior to the blood collection will be recorded on the eCRF. Refer to the separately created procedure for collection, handling, and shipping of blood samples.

Since drug concentrations of subjects in the placebo group will not be measured, the assignment personnel will send an operation manual to the central laboratory to identify samples of subjects in the placebo group. Drug concentration data will be reported to the sponsor after unblinding of the study.

9.1.17.2 Bioanalytical Methods

Plasma concentrations of Lu AA21004 and its metabolites (Lu AA34443 and Lu AA39835) will be analyzed with the validated LC/MS/MS method.

9.1.18 Documentation of Screen Failure Prior to Entrance into Placebo Lead-in Period

For all subjects who signed informed consent and prematurely discontinue the study prior to entry into the placebo lead-in period, the investigator should complete the eCRF. The registration center should be contacted as a notification of screen failure prior to entry into the placebo lead-in period.

The primary reason for screen failure prior to entry into the placebo lead-in period will be recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria <specify the reason.>
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify the reason.>
- Study termination
- Other <specify the reason.>

The identification numbers assigned to subjects who prematurely discontinues prior to entry into the placebo lead-in period should not be reused.

9.1.19 Documentation of Study Entrance into Placebo Lead-in Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria at the start of placebo lead-in period are eligible for entrance into the placebo lead-in period.

If the subject is found to be not eligible for the placebo lead-in period, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.20 Documentation of Screen Failure Prior to Randomization

For all subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization, the investigator should complete the eCRF. The registration center should be contacted as a notification of discontinuation after entry into the placebo lead-in period and prior to randomization.

The primary reason for screen failure after entry into the placebo lead-in period and prior to randomization is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria <specify the reason.>
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify the reason.>
- Study termination
- Other <specify the reason.>

The end-of-study evaluation will be performed for all subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization according to Section 9.3.5.

9.1.21 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization and entrance into the double-blind treatment period.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for screen failure on the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring unused study medication containers (PTP sheets)/unused medications to each dispensing site visit. The dates of the initial and last dosing, as well as any details where a subject takes more or less of the study medications than the specified dose, will be recorded on the eCRF.

If a subject is significantly noncompliant with the study medication (e.g., 6 or more consecutive doses missed), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Period

Informed consent must be obtained prior to the initiation of any study procedures.

The examinations/observations/assessments listed below will be performed at the start of screening period (Days -32 to -12; Visit 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting a subject who prematurely discontinues the study prior to entry into the placebo lead-in period.

- Demographics, medical history, and medication history
- Diagnosis of MDD
- Assessments of the major depressive episode
- Physical examination
- Weight and height
- Vital signs

- Concomitant medications
- Concurrent medical conditions
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Urine drug screening
- ECG procedure
- C-SSRS
- PTE assessment
- MADRS
- HAM-D
- CGI-S

9.3.2 Placebo Lead-in Period

The examinations/observations/assessments listed below will be performed at the start of placebo lead-in period (Day -8 ± 3; Visit 2). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects assessed to be eligible will enter the placebo lead-in period. See Section 9.1.18 for procedures for documenting subjects who prematurely discontinue the study prior to entry into the placebo lead-in period.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- Urine drug screening.
- Blood sampling for pharmacogenomics* (subjects who provided written consent only)
- ECG procedure
- C-SSRS
- PTE assessment
- MADRS
- HAM-D

- CGI-S
- SDS
- DSST
- PDQ-5
- QIDS-J
- Dispense of the study medication (for the placebo lead-in treatment)

* Blood sampling for pharmacogenomics will be performed at the start of placebo lead-in period (Visit 2) or at the earliest possible time during the study.

9.3.3 Start of Double-blind Treatment Period/Randomization

The examinations/observations/assessments listed below will be performed at the start of double-blind treatment period (Day -1; Visit 3). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects assessed to be eligible will be randomized according to Section 8.2 and enter the double-blind treatment period. See Section 9.1.20 for documenting subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization.

The examinations/observations/assessments at Visit 3 should be regarded as baseline evaluations.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- HAM-D
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 2).
- SDS
- DSST

- PDQ-5
- QIDS-J
- Randomization
- Dispense of the study medication (for the double-blind treatment [Inner Carton 1])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

9.3.4 Double-blind Treatment Period

Visit 4

The examinations/observations/assessments listed below will be performed at 1 week after the start of double-blind treatment period (Day 7 ± 1; Visit 4).

- Vital signs
- Concomitant medications
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- DSST
- PDQ-5
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 5

The examinations/observations/assessments listed below will be performed at 2 weeks after the start of double-blind treatment period (Day 14 ± 3; Visit 5).

- Vital signs
- Concomitant medications
- C-SSRS
- PTE/AE assessment

- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 6

The examinations/observations/assessments listed below will be performed at 4 weeks after the start of double-blind treatment period (Day 28 ± 3; Visit 6).

- Weight
- Vital signs
- Concomitant medications.
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Pharmacokinetic sampling
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 7

The examinations/observations/assessments listed below will be performed at 6 weeks after the start of double-blind treatment period (Day 42 ± 3; Visit 7).

- Vital signs

- Concomitant medications
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

9.3.5 End of Double-blind Treatment Period or Early Termination

The examinations/observations/assessments listed below will be performed at 8 weeks after the start of double-blind treatment period (Day 56 ± 3; Visit 8) as evaluation at the end of double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period will be requested to visit the study site for early termination examinations/observations/assessments within 7 days after the day of study discontinuation wherever possible.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- Pharmacokinetic sampling (not performed at early termination)
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- HAM-D
- CGI-S
- CGI-I*

- SDS
- DSST
- PDQ-5
- QIDS-J
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

* The CGI-I score will be assessed comparing with that at Visit 3. However, at early termination prior to Visit 3, the CGI-I score will be assessed by comparing with that at Visit 2.

For all randomized subjects, the investigator must complete the End of Study eCRF page.

After evaluation at the end of double-blind treatment period or early termination, standard therapy may be performed as needed.

9.3.6 Follow-up Period

A safety follow-up assessment will be conducted at 12 weeks after the start of double-blind treatment period (Day 84 ± 5). For subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period, the follow-up assessments will be made 28 ± 5 days after the last dose of the study medication. The follow-up assessments may either be conducted as a visit to the site or as a telephone contact. In the follow-up, the following will be assessed: outcomes of AEs continuing at Visit 8 or early termination visit, new SAEs developing during the follow-up period, and special interest AEs will be assessed. Female subjects of child-bearing potential will be asked to confirm whether they are pregnant or not.

9.3.7 Post Study Care

The study medication will not be available upon completion of the subject’s participation in the study.

9.4 Biological Sample Retention and Destruction

Samples of 5-mL whole blood collected for pharmacogenomics will be stored frozen at the pharmacogenomic specimen storage facility (see the contact listed in the attachment 1; hereinafter referred to as specimen storage facility).

The collected samples will be retained for 20 years from the day when a first pharmacogenomic sample was collected during the study.

When subjects request disposal of a stored sample during the retention period, the site will ask the specimen storage facility to destroy the sample via the sponsor according to the procedure. The specimen storage facility will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents (including medical records) have been destroyed which could identify the subject, and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when pharmacogenomic investigation has been conducted, the remaining sample will be destroyed and the results of pharmacogenomic investigation of the anonymized subject will be retained by the sponsor.

The sponsor will build a management system required for protection of the subject's personal information, define standards for collecting, storage, and destruction of samples, and prepare appropriate procedures.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Of pre-existing conditions (present at the time of signing of informed consent), events that are considered accompanying symptoms of MDD should NOT be recorded as concurrent medical conditions, PTEs, or AEs.
- Other pre-existing conditions are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences an abnormality (e.g., internal bleeding due to blood sampling) associated with the baseline evaluations, the abnormality should be recorded as a PTE and recorded on eCRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). The investigator should ensure that the event term recorded captures the change in the condition (e.g., "worsening of hypertension").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, the investigator should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, the investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. The investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. The investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedures is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures (e.g., cosmetic surgery) performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- All cases of overdose with any medication, including the case without manifested side effects, are considered AEs and will be recorded on the AE page of the eCRF. In addition, cases of overdose will be reported as special interest AEs.

Suicidality events:

- A completed suicide is always captured as an SAE based on its fatal outcome. Furthermore, active suicidal behavior such as suicidal ideation with a specific plan and suicide attempt will also be collected as an SAE.
- Unless the event in question meets the definition of "serious," suicidal thoughts or suicidal ideation without a specific plan or action will be collected as a non-serious AE in accordance with the standard AE reporting requirements.
- A subject who presents with self-mutilation should be asked by the investigator to clarify whether the subject was attempting suicide. If the subject was attempting suicide, the behavior will be collected as an SAE, and the specific suicidal behavior (e.g., wrist cutting) will be recorded in the eCRF. If the subject was not attempting suicide, the behavior will be collected as a non-serious AE in accordance with the standard AE reporting requirements.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.*
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

* The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including seizure and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial lung disease)
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death
	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxin shock

The following events are also to be considered SAEs.

- Completed suicide
- Active suicidal ideation
- Active suicidal behavior such as suicide attempt
- Self-injury with suicide attempt

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) is 1 of scientific and medical concern specific to the compound or program. In this study, skin reaction, allergic reaction, hepatic impairment, and overdose are defined as special interest AEs. Ongoing monitoring and communication by the investigator to Takeda may be appropriate, and if the events occur, they will be reported according to Section 10.2.1.3. Such events may require further investigation in order to characterize and understand them.

10.1.5.1 Skin and Allergic Reaction

When the causal relationship between rash or allergic reaction and the study medication is assessed as probable or possible, rash or allergic reaction will be reported as a special interest AE according to Section 10.2.1.3 after the nature and the site are characterized. When the causal relationship between rash or allergic reaction and the study medication is assessed as not related, rash or allergic reaction is not required to be reported as a special interest AE.

When rash or allergic reaction develops, the subject should be adequately examined for any clinical features that may suggest the development of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome (SJS). In addition, the subject should be monitored for the appearance of any of the following signs:

a) Involvement of mucous membrane or the conjunctiva

b) Development of skin pain

c) Urticaria, blistering, or other types of skin lesions

d) Angioedema

If a subject presents with symptoms of a systemic reaction (e.g., generalized rash), or signs of severe rash, or if it is clinically necessary, the following laboratory parameters should also be investigated and monitored accordingly: complete blood count with differentials, liver and renal function tests, and urinalysis. If deemed necessary by the investigator, subjects should be received examination by a dermatologist, and photographs of the skin rash and/or skin biopsies will be obtained as needed.

10.1.5.2 Hepatic Impairment

If a subject has ALT or AST >3 × ULN, and follow-up laboratory tests (see Section 9.1.12) also shows ALT or AST >3 × ULN, it should be reported as a special interest AE according to Section 10.2.1.3. In addition, the relevant subject details and possible alternative etiologies other than the study medication should be investigated.

If the abnormality falls under a drug-induced liver function abnormality that may lead to severe hepatic impairment (see Section 10.2.3), it should also be reported as an SAE.

10.1.5.3 Overdose

For overdose, refer to Section 8.1.4. All cases of overdose will be documented as AEs on an AE page of the eCRF and should be reported as special interest AEs according to Section 10.2.1.3 (with or without associated adverse events).

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Probable:	An AE that has a strong temporal relationship to the study medication(s), or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
Possible:	An AE that has a suggestive temporal relationship to the study medication(s), and an alternative etiology is equally or less likely.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of the study medication(s) or that can reasonably be explained by other factors, such as underlying diseases, concurrent medical conditions, concomitant drugs and concurrent treatments (that is, there is no causal relationship between the study medication and the AE).

An AE is considered causally related to the use of the study medication when the causality assessment is *probable* or *possible*.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs. The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of AEs/PTEs will be determined based on the criteria described below.

AE/PTE	Start Date
Signs, symptoms, and diseases (diagnosis)	Date when the subject or the investigator first notices the sign or symptom of the AE
Asymptomatic disease	Date when a definite diagnosis is determined based on the results of diagnostic testing. Even if obsolete findings are indicated based on the test findings or the approximate time of onset can be estimated, the date when a definite diagnosis is made should be recorded.
Worsening of concurrent medical conditions or PTEs	Date when the subject or the investigator first notices worsening of the disease or symptom.
Normal in the initial assessment after signing of informed consent but abnormal in the subsequent assessment (for PTEs) Abnormal in the assessment after the start of the study medication (for AEs)	Date when the test is performed in which a clinically significant abnormal test value is observed
Abnormal in the initial assessment after signing of informed consent and has worsened in the subsequent assessment (for PTEs) Abnormal in the assessment at the start of the study medication and has worsened in the subsequent assessment (for AEs)	Date when the test is performed in which a medically significant elevation, reduction, increase or decrease in clinical laboratory test values is observed

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The AE/PTE not determined to have resolved at the end of the study is assessed as ongoing

10.1.11 Frequency

Episodic AEs/PTEs (e.g., constipation, diarrhea, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Medication

The action taken for the study medication is classified and defined as follows:

Drug withdrawn	The study medication is stopped due to the particular AE (including withdrawal at the subject's discretion).
Dose not changed	The dose is not changed even after the occurrence of the particular AE. This shall apply in case the study medication is stopped due to another AE. This shall also apply, for example, in case the study medication is stopped for any reason other than intervention for the particular AE, such as the subject's negligence.

Unknown	For example, attempts to contact the subject are unsuccessful and the course of the particular AE after the start date cannot be followed.
Not Applicable	For example, the study medication has already been completed or stopped before the onset of the particular AE.

10.1.13 Outcome

The outcome of AEs/PTEs is classified as follows:

Category	Assessment Criteria
Recovered/Resolved	• The symptom or finding has disappeared or resolved. • The abnormal laboratory value has improved to the normal range or to the level at baseline (for AEs) or at the first assessment after signing of informed consent (for PTEs).
Recovering/Resolving	• The intensity is lowered by at least 1 grade. • The symptom or finding has almost disappeared. • The abnormal laboratory value has improved, but not to the normal range or the level at baseline (for AEs) or at the first assessment after signing of informed consent (for PTEs). • The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (no need to record the date of death).
Not recovered/not resolved	• There is no change in the symptom, finding, or laboratory value. • The intensity of the symptom, finding, or laboratory value on the last day of the observed period has got worsen than when it started. • An irreversible congenital anomaly. • The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" AE/PTE (no need to record the date of death).
Resolved with sequelae	• The subject recovered from an acute AE/PTE but was left with impairment that interferes with the subject's daily life.
Fatal	• There is a direct relationship between the death and the AE/PTE. • The direct relationship indicates that the AE/PTE caused or apparently contributed to the death. • The outcome of another AE/PTE reported in the same subject that is not determined (considered or estimated) as the cause of the death is not assessed as "fatal." • If the outcome is "fatal," the date of death should be recorded.
Unknown	• The course of the AE/PTE after the start date cannot be followed up as specified in the protocol due to hospital change or residence change.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication in the

placebo lead-in period. For subjects who discontinue prior to the first study medication administration in the placebo lead-in period, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication in the placebo lead-in period. Routine collection of AEs will continue until Visit 8 or Early Termination Visit.

Collection of SAEs or special interest AEs will continue until the end of the follow-up period.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the change (for permanent or irreversible PTEs). Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the change (for permanent or irreversible AEs). All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date
3. Frequency
4. Severity
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (probable, possible, not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs)
8. Outcome of event
9. Seriousness
10. Classification as special interest AEs (Yes or No)

C-SSRS will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. If it is determined that an AE not previously reported has been identified through this follow-up, normal reporting requirements should be applied.

AEs and serious PTEs will be followed up until resolution or until the investigator judges that further follow-up is not necessary.

10.2.1.3 Special Interest AE Reporting

If the special interest AE (refer to Section 10.1.5) occurs through the AE collection period, it should be reported to Safety Information Emergency Call Center, in principle (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The investigator should complete the Rash and Allergic Reaction, Hepatic Impairment or Overdose Form within 10 business days and report to Safety Information Emergency Call Center, in principle. In addition, the investigator should submit to the sponsor the original Rash and Allergic Reaction, Hepatic Impairment or Overdose Form.

The special interest AEs have to be recorded as AEs in the eCRF.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure. PTEs that fulfill the serious criteria described in Section 10.1.4 are also to be considered SAEs and should be reported in the same manner.

The investigator should report the SAEs with information required in the SAE form to Safety Information Emergency Call Center, in principle, within 1 business day of the first onset or subject's notification of the event. The investigator should prepare the completed SAE form within 10 calendar days and submit to Safety Information Emergency Call Center, in principle. In addition, the investigator should submit to the sponsor the original SAE form.

For the report within 1 business day, the information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be also reported to the sponsor if considered related to study participation. Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the investigator must contact the sponsor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests must also be performed (see Section 9.1.12). If the investigator considers that such liver function abnormality cannot be explained by any factor other than the study medication, the event should be reported as a SAE (see Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the detailed report becomes available at a later date, the investigator should complete a follow-up SAE form copy or provide other written documentation and report it immediately to the sponsor or Safety Information Emergency Call Center. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and the head of the study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee (CRO), SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of the study medication or that would be sufficient to consider changes in the administration of study medication or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff (the investigator, subinvestigators, and other study collaborators) in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The investigator must review the eCRFs for completeness and accuracy and must sign the appropriate eCRFs. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs.

- Laboratory test values measured at the central laboratory
- Observed drug concentrations

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail,

and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS), and safety analysis set.

The FAS, which will be used as a primary analysis set for efficacy analysis, is defined as "all subjects who were randomized and received at least 1 dose of the study medication in the double-blind treatment period."

The exact definition of each analysis set is specified in the Data Handling Rules for Statistical Analysis.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Data Handling Rules for Statistical Analysis must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Major background and demographic characteristics will be summarized overall and by treatment group.

13.1.3 Efficacy Analysis

Primary Efficacy Analysis for Primary Endpoint

The primary endpoint for this study is the change from baseline (i.e. at the start of double-blind treatment period) in the MADRS total score after 8 weeks of treatment.

Comparisons between each Lu AA21004 treatment group and the placebo group at Week 8 of the double-blind treatment period will be performed using the FAS based on MMRM analysis of covariance with the change from baseline in the MADRS total score as a dependent variable, and visit, treatment group, visit-by-treatment group interaction and baseline MADRS total score-by-visit interaction as fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom. Holm's step down method will be used to adjust the multiplicity for the comparisons. More specifically, let H_{01}, H_{02} be a family of hypotheses as follows:

H_{01}: $\mu_{Placebo} = \mu_{10\ mg}$

H_{02}: $\mu_{Placebo} = \mu_{20\ mg}$

Then let P_1 and P_2 denote the unadjusted p-values of tests for H_{01} and H_{02}, respectively. Order the p-values from the smallest to the largest, $P^{(1)}$, $P^{(2)}$ and let the corresponding null hypotheses be $H^{(1)}$, $H^{(2)}$. Holm's step-down method proceeds as follows:

Step 1: if $P^{(1)} > 0.025$, retain both null hypotheses $H^{(1)}$ and $H^{(2)}$, and stop. If $P^{(1)} \leq 0.025$, reject null hypothesis $H^{(1)}$ and go to Step 2.

Step 2: if $P^{(2)} > 0.05$, retain null hypothesis $H^{(2)}$. If $P^{(2)} \leq 0.05$, reject null hypothesis $H^{(2)}$.

Secondary Efficacy Analyses for Primary Endpoint

To check the robustness of the results, the same analysis as used for the primary efficacy analysis will be performed using the PPS.

For the FAS, an analysis of covariance (ANCOVA) model with the change from baseline in the MADRS total score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) as a dependent variable, treatment group as a fixed effect and the baseline MADRS total score as a covariate will be applied for comparisons between the placebo group and each Lu AA21004 treatment group.

Analyses for Secondary Endpoints

MADRS response (MADRS response is defined as a ≥50% decrease from baseline in the MADRS total score) and MADRS remission (MADRS remission is defined as the MADRS total score ≤10) after 8 weeks of treatment (LOCF) will be compared between treatment groups using logistic regression analysis including the baseline MADRS total score and treatment groups in the model.

The change from baseline in the HAM-D17 total score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline HAM-D17 total score as a covariate.

The CGI-I score after 8 weeks of treatment (LOCF) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline CGI-S score as a covariate.

The change from baseline in the CGI-S score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline CGI-S score as a covariate.

The change from baseline in the SDS score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline SDS score as a covariate.

The change from baseline in the DSST score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline DSST score as a covariate.

The change from baseline in the PDQ-5 score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline PDQ-5 score as a covariate.

Two-sided tests with significance level at 5% will be used for all statistical tests. Ninety-five percent confidence intervals will be presented along with the P-values.

13.1.4 Pharmacokinetic Analysis

The population pharmacokinetic analysis of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 will be performed using the nonlinear mixed effect model (NONMEM). Pharmacokinetic parameters of individual subjects (e.g., AUC[0-tau], Cavg, Cmax) will be estimated and their correlation with relevant pharmacodynamic parameters (efficacy and tolerability/safety) will be explored. The population pharmacokinetic analysis plan will be prepared separately.

13.1.5 Safety Analysis

AEs

The definition of treatment-emergent adverse events (TEAE) will be described in the statistical analysis plan (SAP). TEAEs will be summarized using the safety analysis set. TEAEs will be coded using the MedDRA and will be summarized by system organ class (SOC) and preferred term (PT). No statistical testing or inferential statistics will be generated.

A subject who has developed a same TEAE more than once will be counted as 1 subject in the severity category corresponding to the maximum severity of the event.

Clinical Laboratory Test, Weight, Vital Signs, and ECG

Summary statistics of observed values and changes at each time point (values at each time point in the double-blind treatment period − baseline) will be calculated for clinical laboratory tests, vital signs, ECG parameters, and weight for each treatment group. Incidences of values that are outside normal ranges and are potentially and clinically significant will be calculated.

C-SSRS

Descriptive statistics of C-SSRS will be calculated at each time point for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A number of subjects planned to be enrolled in this study is 480 (160 per group). Assuming the true mean differences of 3.5 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between each Lu AA21004 group and the placebo group by 2-sample t-test. In addition, assuming the true mean differences of 3.0 for the change from baseline

in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between either the Lu AA21004 10 mg or 20 mg group and the placebo group. These power calculations assume a common standard deviation of 9.5 for the change from baseline in the MADRS total score, with a 2-sided level of 0.025.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, and informed consent documentation. It is important that the investigator, the subinvestigator, and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or signing of informed consent). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug no protocol activities, including the informed consent procedure may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

Regarding pharmacogenomic investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for pharmacogenomics investigations, and a research protocol will require prior approval of the company IRB in Japan.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by the IRB prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent form must be signed and/or sealed, and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign and/or seal using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and/or seal, and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed and/or sealed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. A copy of the signed and/or sealed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

The informed consent form for pharmacogenomic research in the clinical study of Lu AA21004 will be used to explain the pharmacogenomic research to subjects after explanation of the informed consent for the entry into the study. Pharmacogenomic samples will be collected from subjects who have consented to both the study and the pharmacogenomic research.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites (JAPIC-CTI) before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (JAPIC-CTI), as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Nakane Y, Arima K. Cause and Symptom of Depression. The Journal of Practical Pharmacy. 2000;51(2):826-34.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Translated by Takahashi S, Ono Y, Someya T. Igaku-Shoin. 2004.

[3] Guideline for Clinical Evaluation of Antidepressants (Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division; Notification No.1116-1 dated November 16 in 2010) (in Japanese).

[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Translated by Takahashi S, Ono Y, Someya T, Kanba S, Ozaki N, Mimura M, Murai T.. Igaku-Shoin. 2014.

[5] Bialik RJ, Ravindran AV, Bakish D, Lapierre YD., 1995. A Comparison of Placebo Responders and Nonresponders in Subgroups of Depressive Disorder. J Psychiatry Neurosci. 1995;20:265-70.

[6] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

[7] Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278-96.

[8] Guy W. ECDEU Assessment Manual for Psychopharmacology (Revised). Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health, Psychopharmacology Research Branch; 1976. p.193-198

[9] Olfson M, Fireman B, Weissman MM, Leon AC, Sheehan DV, Kathol RG, et al. Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry. 1997;154:1734-40.

[10] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. Am J Psychiatry. 2007;164(7):1035-43.

[11] Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the Assessment of Suicidality in Youth. CNS Spectr. 2007;12(2):156-62.

Appendix A Schedule of Study Procedures

	Screening Period	Placebo Lead-in Period [a]	Double-blind Treatment Period						Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET [c]**	**Follow-up [d]**
Week [b]	-4 to -2	-1	0	1	2	4	6	8/ET [c]	12 [d]
Day [b]	-32 to -12	-8	-1	7	14	28	42	56/ET [c]	84 [d]
Visit Window (Days) [b]	-	±3	0	±1	±3	±3	±3	±3/-	±5
Informed consent	X [e]								
Inclusion/exclusion criteria	X	X [f]	X [f]						
Demographics, medical history, medication history	X								
Diagnosis of MDD	X								
Assessments of major depressive episode	X								
Physical examination	X	X	X					X	
Weight, height [g]	X	X	X			X		X	
Vital signs	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	
Concurrent medical conditions	X								
Clinical laboratory tests [h]	X	X	X			X		X	
Pregnancy test [i]	X	X	X			X		X	(-)
Urine drug screening	X	X							
Pharmacokinetic sampling						X		(X)	
Pharmacogenomic sampling [j]		(X)							
ECG	X	X	X			X		X	
C-SSRS	X	X	X	X	X	X	X	X	
PTE/AE assessment [k]	X	X	X	X	X	X	X	X	(-)
<Assessments with Rating Scales>									
MADRS	X	X	X	X	X	X	X	X	
HAM-D	X	X	X					X	
CGI-S	X	X	X	X	X	X	X	X	
CGI-I [l]			X	X	X	X	X	X	
SDS		X	X					X	
DSST		X [m]	X	X				X	
PDQ-5		X	X	X				X	
QIDS-J		X	X	X	X	X	X	X	
<Clinical Supply>									
Randomization			X						
Dispense study medication [n]		X	X	X	X	X	X		
Drug return/accountability/compliance			X	X	X	X	X	X	

ET = early termination

(a) In the placebo lead-in period, subjects will receive the study medication in a single-blind manner.
(b) The visit day in the double-blind treatment period is defined as Week 0 (Day -1). The day after Day -1 is defined as Day 1. All visit windows are in reference to the date of scheduled visit.
(c) Subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period will be requested to visit the study site for the end-of study examinations within 7 days after the day of study discontinuation, wherever possible, and will be assessed in the same way as at Visit 8 (except for blood sampling for pharmacokinetics).
(d) Safety follow-up assessments will be conducted. For subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period, the follow-up assessments will be made 28 ± 5 days after the last dose of the study medication. The follow-up assessments can either be conducted as a visit to the site or as a telephone contact. In the follow-up, the following will be assessed: outcomes of AEs continuing at Visit 8 (or the end-of study assessments if administration of the study medication is discontinued), new SAEs developed during the follow-up period, and special interest AEs. Female subjects of child-bearing potential will be asked to confirm whether they are pregnant or not.
(e) Informed consent must be obtained prior to the initiation of any study procedure including washout of excluded medications. Informed consent may be obtained prior to the visit window of Visit 1.
(f) Update at Visits 2 and 3.
(g) Height is measured at only Visit 1.
(h) Clinical laboratory tests will be performed under fasted conditions at Visits 2, 3 and 8 or Early Termination Visit, and at other visits wherever possible.
(i) For women of child-bearing potential.
(j) Only for subjects who consent to provide pharmacogenomic samples, separately from consent of participation in the study. Pharmacogenomic samples for analyses will be collected at Visit 2 or thereafter, as soon as possible, during the study.
(k) PTEs will be collected prior to study medication administration in the placebo lead-in period, and AEs will be collected after study medication administration.
(l) The CGI-I score will be assessed by comparison with that at Visit 3. However, at Visit 3 or early termination prior to Visit 3, the score will be assessed by comparison with that at Visit 2.
(m) Subjects will complete the sample items prior to the actual test.
(n) At Visit 2, subjects will be dispensed the study medication for the placebo lead-in period. At Visit 3, subjects will be dispensed the study medication for the double-blind treatment period, Inner Carton 1, and Inner Carton 2 at Visits 4 to 7, with a necessary and sufficient amount of the study medication by next visit.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety, and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications, and responsibilities of individual personnel to the investigator and the study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing, and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of an SAE, immediately notify the director of the site and the sponsor in writing.
11. Determine the need of emergency key code blinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
14. Discuss any proposal from the sponsor including update of the protocol.
15. Notify the director of the site of the end of the study in writing.

Appendix C Detailed Description of Amendments to Text

The following describes changes from the initial protocol.

Page 8, Section 2.0 STUDY SUMMARY, Study Design
(Page 22, Section 6.1 Study Design)

Existing Text

This study consists of a *2*-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week follow-up period…

Revised Text

This study consists of a **1-to 3**-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period, and a 4-week follow-up period…

Rationale for Amendment

Correction for appropriate description.

Page 9, Section 2.0 STUDY SUMMARY, Period of Evaluation

Existing Text

15 weeks in total
Screening period: *2* weeks
Placebo lead-in period: 1 week
Double-blind treatment period: 8 weeks
Safety follow-up period: 4 weeks

Revised Text

14 to 16 weeks in total
Screening period: **1 to 3** weeks
Placebo lead-in period: 1 week
Double-blind treatment period: 8 weeks
Safety follow-up period: 4 weeks

Rationale for Amendment

Correction for appropriate description.

Page 12, Section 3.0 LIST OF ABBREVIATIONS

Existing Text

NSAIDs *non-steroid* anti-inflammatory drug

PDQ Perceived Deficits *Questionaire*

Revised Text

NSAIDs **non-steroidal** anti-inflammatory drug

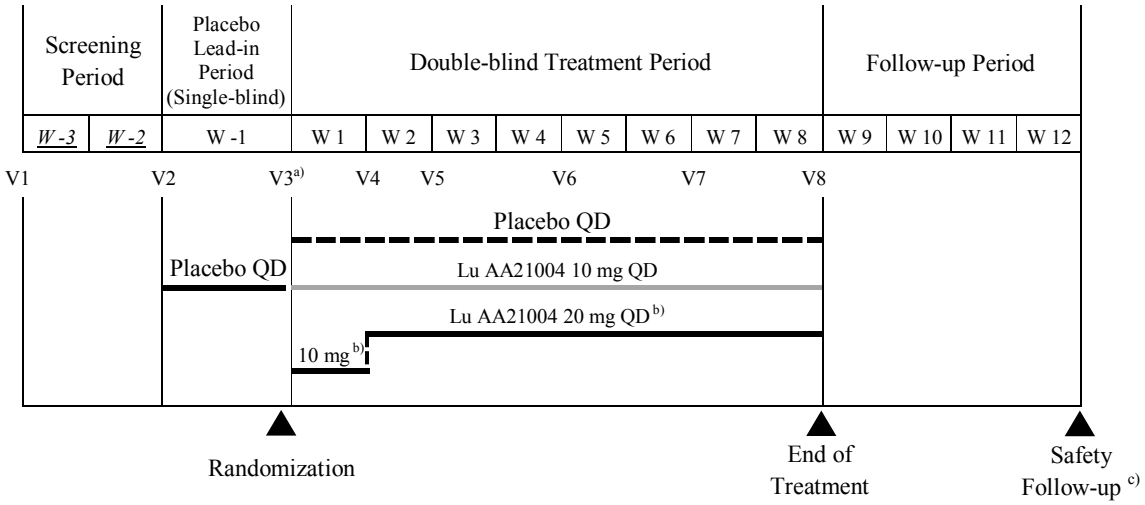
PDQ Perceived Deficits **Questionnaire**

Rationale for Amendment

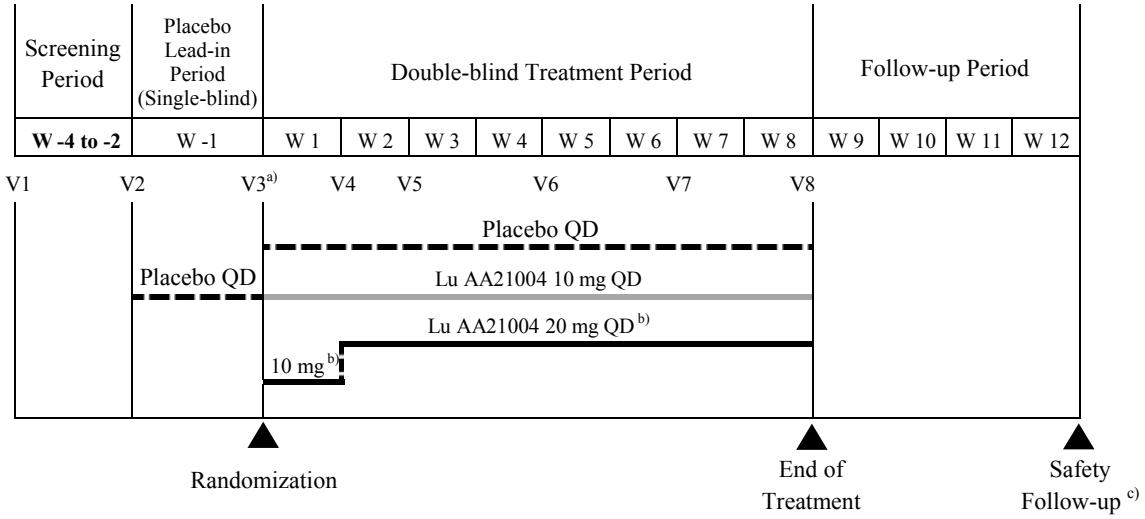
Correction of erroneous description.

Page 21, Section 6.1 Study Design, Figure 6.a Schematic of Study Design

Existing Text



Revised Text



Rationale for Amendment

Correction for appropriate description.

Page 28, Section 7.3 Excluded Medications and Treatments, Table 7.a List of Prohibited or Restricted Concomitant Drugs, (4) Hypnotics

Existing Text

Non-benzodiazepines (zolpidem, zopiclone, and eszopiclone) are allowed. However, use of these drugs should be kept to the minimum necessary, and use for 2 consecutive days and use at the night before a study visit are NOT allowed. In addition, the type and dose of non-benzodiazepines should NOT be changed from the start of placebo lead-in period (Visit 2) to the end of double-blind treatment period (Visit 8) or early termination.

Revised Text

Non-benzodiazepines (zolpidem, zopiclone, and eszopiclone) are allowed. However, use of these drugs should be kept to the minimum necessary, and use for 2 **or more** consecutive days and use at the night before a study visit are NOT allowed. In addition, the type and dose of non-benzodiazepines should NOT be changed from the start of placebo lead-in period (Visit 2) to the end of double-blind treatment period (Visit 8) or early termination.

Rationale for Amendment

Correction of an omission.

Page 31, Section 7.4, Diet, Fluid, and Activity Control

Existing Text

7. The subject must visit the site under fasted conditions at Visits 3 and 8 or Early Termination Visit. For visit serum chemistry test is scheduled, the subject visits the site under fasted conditions wherever possible.

Revised Text

7. The subject must visit the site under fasted conditions at Visits **2,** 3 and 8 or Early Termination Visit. For visit serum chemistry test is scheduled, the subject visits the site under fasted conditions wherever possible.

Rationale for Amendment

Correction of an omission.

Page 40, Section 9.1.5 Physical Examination Procedure

Existing Text

All subsequent physical examinations *after administration of the study medication in the double-blind treatment period* should assess clinically significant changes from the examinations *at the start of double-blind treatment period (Visit 3)*.

Revised Text

All subsequent physical examinations should assess clinically significant changes from the examinations **prior to first dose**.

Rationale for Amendment

Correction of erroneous description.

Page 40, Section 9.1.8.1 Rating and Rating Training for MDD Montgomery-Åsberg Depression Rating Scale (MADRS)

Existing Text

The MADRS will be used for a primary efficacy measurement. The MADRS is a depression rating scale consisting of 10 items representing the core symptoms of depression.[6] The MADRS is rated using Structured Interview Guide for MADRS (SIGMA). The rating should be based on a clinical interview with the subject, moving from broadly phrased questions about symptoms to more detailed questions. The rating is performed based on the most severe condition of the subject during the past 1 week, and each item is rated from 0 to 6. *Items 2 to 10* are based upon subject report, and *Item 1* is based on the observation of the subjects...

Revised Text

The MADRS will be used for a primary efficacy measurement. The MADRS is a depression rating scale consisting of 10 items representing the core symptoms of depression.[6] The MADRS is rated using Structured Interview Guide for MADRS (SIGMA). The rating should be based on a clinical interview with the subject, moving from broadly phrased questions about symptoms to more detailed questions. The rating is performed based on the most severe condition of the subject during the past 1 week, and each item is rated from 0 to 6. **Item 1 and Items 3 to 10** are based upon subject report, and **Item 2** is based on the observation of the subjects...

Rationale for Amendment

Correction of erroneous description.

Page 44, Section 9.1.12 Procedures for Clinical Laboratory Samples, Table 9.a Clinical Laboratory Tests

Existing Text

Hormonal Test
Thyroid stimulating hormone (TSH)
Free T_4 [b)]

b) When TSH value is outside the normal range, free T_4 will be measured. If a clinically significant abnormality of thyroid gland is found based on the results of TSH and free T_4, the subject will be excluded from the study.

Revised Text

Hormonal Test (Visit 1 only)
Thyroid stimulating hormone (TSH) [b)]
Free T_4 [b)]

b) **TSH will be measured at Visit 1, and** when TSH value is outside the normal range, free T4 will be measured. If a clinically significant abnormality of thyroid gland is found based on the results of TSH and free T4, the subject will be excluded from the study.

Rationale for Amendment

Correction of omissions.

Page 44, Section 9.1.12 Procedures for Clinical Laboratory Samples, Table 9.a Clinical Laboratory Tests

Existing Text

a) Blood will be collected under fasted conditions at Visits 3 and 8 or Early Termination Visit. For other visits, blood will be collected under fasted conditions wherever possible.

Revised Text

a) Blood will be collected under fasted conditions at Visits **2,** 3 and 8 or Early Termination Visit. For other visits, blood will be collected under fasted conditions wherever possible.

Rationale for Amendment

Correction of an omission.

Page 48, Section 9.3.1 Screening

Existing Text

The examinations/observations/assessments listed below will be performed at the start of the screening period (*Day -22 ± 10*; Visit 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting a subject who prematurely discontinues the study prior to entry into the placebo lead-in period.

Revised Text

The examinations/observations/assessments listed below will be performed at the start of the screening period (**Day -32 to -12**; Visit 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting a subject who prematurely discontinues the study prior to entry into the placebo lead-in period.

Rationale for Amendment

Correction for appropriate description.

Page 49, Section 9.3.2 Placebo Lead-in Period

Existing Text

- Clinical laboratory tests

Revised Text

- Clinical laboratory tests **(fasted)**

Rationale for Amendment

Correction of an omission.

Page 70, Section 13.1.1 Analysis Sets

Existing Text

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Data Handling Rules for Statistical Analysis must be finalized *prior to unblinding*.

Revised Text

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Data Handling Rules for Statistical Analysis must be finalized **prior to database lock**.

Rationale for Amendment

Correction of erroneous description.

Page 80, Appendix A Schedule of Study Procedures

Existing Text

	Screening Period
Visit Number	**1**
Week [(b)]	*-3*
Day [(b)]	*-22*
Visit Window (Day) [(b)]	*±10*

Revised Text

	Screening Period
Visit Number	**1**
Week [(b)]	**-4 to -2**
Day [(b)]	**-32 to -12**
Visit Window (Day) [(b)]	-

Rationale for Amendment

Correction for appropriate description.

Page 81, Appendix A Schedule of Study Procedures

Existing Text

(h) Clinical laboratory tests will be performed under fasted conditions at Visits 3 and 8 or Early Termination Visit, and at other visits wherever possible.

Revised Text

(h) Clinical laboratory tests will be performed under fasted conditions at Visits **2,** 3 and 8 or Early Termination Visit, and at other visits wherever possible.

Rationale for Amendment

Correction of an omission.

PROTOCOL

<Title>

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Evaluate the Efficacy and Safety of Once Daily Oral Lu AA21004 in Patients with Major Depressive Disorder

<Short Title>

A Phase III Study of Lu AA21004 in Patients with Major Depressive Disorder

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi		
Study Number:	Lu AA21004/CCT-004		
Edition:	Initial Protocol		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Lu AA21004		
Date:	9 January 2015		

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

Refer to the attachment.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** Lu AA21004	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Evaluate the Efficacy and Safety of Once Daily Oral Lu AA21004 in Patients with Major Depressive Disorder	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: Lu AA21004/CCT-004	**Phase:** 3	

Study Design:

This is a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the efficacy and safety of 8-week treatment of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) in Japanese subjects with major depressive disorder (MDD).

This study consists of a 2-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week safety follow-up period. Subjects who fulfill all inclusion criteria and none of exclusion criteria at the start of screening period (Visit 1) and at the start of placebo lead-in period (Visit 2) will move into the placebo lead-in period and receive placebo once daily for 1 week in a single-blind manner. Afterwards, these who fulfill all the inclusion criteria and none of the exclusion criteria at the start of double-blind treatment period (Visit 3) will move into the double-blind treatment period and will be randomized in a 1:1:1 ratio to one of the following treatment groups: the placebo group, the Lu AA21004 10 mg/day group or the Lu AA21004 20 mg/day group. Subjects in the placebo group and the Lu AA21004 10 mg/day group will receive placebo and Lu AA21004 10 mg, respectively, once daily from the day after Visit 3 for 8 weeks in a double-blind manner. Subjects in the Lu AA21004 20 mg/day group will receive Lu AA21004 10 mg once daily from the day after Visit 3 for 1 week and thereafter Lu AA21004 20 mg once daily for 7 weeks in a double-blind manner. Subjects in any treatment groups will visit study sites at Week 1, 2, 4, 6 and 8 during the double-blind treatment period for examinations/observations/assessments.

A safety follow-up contact (visit or phone call) will be made 4 weeks after the completion of the double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or the double-blind treatment period will be requested to visit the study site for the end-of study assessments within 7 days after the discontinuation decision is made wherever possible, and will be contacted 4 weeks after the last dose of the study medication for safety follow-up.

Primary Objective:

- To evaluate the efficacy of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.

Secondary Objectives:

- To evaluate the safety and tolerability of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.
- To evaluate the efficacy of Lu AA21004 (10 or 20 mg/day) on cognitive functions after 8 weeks of treatment in Japanese patients with MDD.

Additional Objective:

- To analyze the plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 using population pharmacokinetic analyses.

Subject Population:

Male and female subjects, aged between 20 and 75 years (both inclusive), with recurrent MDD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria.

Number of Subjects:	**Number of Sites:**
Randomized subjects: 480 (160 per group)	Approximately 60 sites
Dose Levels: Placebo lead-in period: Placebo once daily Double-blind treatment period: Lu AA21004 (10 or 20 mg) or placebo once daily	**Route of Administration:** Oral
Duration of Treatment: 9 weeks in total Placebo lead-in period: 1 week Double-blind treatment period: 8 weeks	**Period of Evaluation:** 15 weeks in total Screening period: 2 weeks Placebo lead-in period: 1 week Double-blind treatment period: 8 weeks Safety follow-up period: 4 weeks

Main Criteria for Inclusion:

- The subject suffers from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x).
- The subject is a man or a woman aged 20 to 75 years (both inclusive) at the time of informed consent.
- The reported duration of the current major depressive episode is 3 to 12 months (both inclusive) at the start of screening period.
- The subject has a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26, a Hamilton Depression Rating Scale (HAM-D17) total score ≥18, and a clinical global impression scale-Severity (CGI-S) score ≥4 at the start of screening period, the start of placebo lead-in period and the start of the double-blind treatment period.

Main Criteria for Exclusion:

- The subject has any following current or past history of psychiatric disorder and/or neurological disorder:
  - Any current psychiatric disorder other than MDD as defined by DSM-IV-TR (To be assessed by Mini International Neuropsychiatric Interview: MINI). A subject who exhibits symptoms of anxiety is eligible unless the subject fulfills the diagnostic criteria for a current anxiety disorder per DSM-IV-TR.
  - Current diagnosis or history of manic, mixed or hypomanic episode, MDD with psychotic features, schizophrenia or any other psychotic disorder (including substance-related mental disorders, or mental disorders due to a general medical condition) as defined by DSM-IV-TR.
  - Current diagnosis or history of any substance-related disorder (except nicotine and caffeine-related disorders) as defined by DSM-IV-TR.
  - The subject with a positive urine drug screening result at the start of screening period or the start of placebo lead-in period. In case that a subject showed positive test result at the start of screening period because the test was conducted before washout of pretreatment drugs, the subject is eligible as long as he/she shows negative result at the start of placebo lead-in period.
  - Presence or history of any clinically significant neurological disorder (including epilepsy).
  - Any neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).
  - Any DSM-IV-TR axis II disorder.
- The subject has the current or previous major depressive episode which were considered by the investigator to have been resistant to 2 or more adequate antidepressants treatments of at least 6 weeks duration each at sufficient doses.

- The subject has received any augmentation therapy (e.g. lithium, T3/T4, lamotrigine, sodium valproate, carbamazepine, additional atypical antipsychotic, or concomitant use of other antidepressant, etc.) for the current major depressive episode.
- In the opinion of the investigator, the subject has experienced significant number of major depressive episodes in the past, and is suspected of disease other than MDD.
- In the opinion of the investigator, the subject has experienced the first major depressive episode at his/her young age, and is suspected of disease other than MDD.
- The subject has a MADRS total score at the start of double-blind treatment period that has improved or aggravated by 25% or more from the score at the start of placebo lead-in period.
- The subject is at significant risk of suicide or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS at the start of screening period, the start of placebo lead-in period or the start of double-blind treatment period, or has attempted suicide within 6 months prior to the start of screening period.
- The subject has experienced any environmental change (e.g. temporary retirement, returnment, change of residence) considered by the investigator to have the potential to impact on the efficacy evaluation, or plans such environmental changes during the study.
- The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, neoplastic, skin and subcutaneous tissue disorders, eye disorders, or metabolic disturbance.

Main Criteria for Evaluation and Analyses:

Efficacy Endpoints

Primary Endpoint

- Change from baseline (i.e. at the start of double-blind treatment) in the MADRS total score after 8 weeks of treatment

Secondary Endpoints

- MADRS response after 8 weeks of treatment (last observation carried forward [LOCF])
  (MADRS response is defined as a ≥50% decrease in the MADRS total score from baseline).
- MADRS remission after 8 weeks of treatment (LOCF)
  (MADRS remission is defined as the MADRS total score of ≤10).
- Change from baseline in the HAM-D17 total score after 8 weeks of treatment (LOCF).
- Clinical global impression scale-Improvement (CGI-I) score after 8 weeks of treatment (LOCF).
- Change from baseline in the CGI-S score after 8 weeks of treatment (LOCF).
- Change from baseline in the Sheehan Disability Scale (SDS) total score after 8 weeks of treatment (LOCF).
- Change from baseline in the Digit Symbol Substitution Test (DSST) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Perceived Deficits Questionnaire (PDQ-5) score after 8 weeks of treatment (LOCF).

Pharmacokinetic Endpoint

- Plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835.

Safety Endpoints

- Adverse events
- Weight
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Considerations:

Change from baseline (i.e. the start of double-blind treatment period) in the MADRS total score after 8 weeks of treatment is the primary efficacy endpoint. Comparisons between each Lu AA21004 treatment group and the placebo group at Week 8 of the double-blind treatment period will be performed using the full analysis set (FAS) based on Mixed Model for Repeated Measures (MMRM) analysis of covariance with the change from baseline in the MADRS total score as a dependent variable, and visit, treatment group, visit-by-treatment group interaction and baseline MADRS total score-by-time point interaction as fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom. Holm's step-down method will be used to adjust the multiplicity for the comparisons.

Sample Size Justification:

A number of subjects planned to be enrolled in this study is 480 (160 per group). Assuming the true mean differences of 3.5 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between each Lu AA21004 group and the placebo group by 2-sample t-test. In addition, assuming the true mean differences of 3.0 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between either the Lu AA21004 10 mg or 20 mg group and the placebo group. These power calculations assume a common standard deviation of 9.5 for the change from baseline in the MADRS total score, with a 2-sided level of 0.025.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ANCOVA	analysis of co-variance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
Cavg	average plasma concentration at steady state
CGI-I	clinical global impression scale-Improvement
CGI-S	clinical global impression scale-Severity
Cmax	maximum observed plasma concentration
COX	cyclooxygenase
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P-450
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSST	Digit Symbol Substitution Test
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transferase
HAM-D	Hamilton Depression Rating Scale
hCG	Human chorionic gonadotropin
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation
INR	international normalized ratio
LDL	low-density lipoprotein
LOCF	Last Observation Carried Forward
MADRS	Montgomery Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model for Repeated Measures
NaSSA	noradrenergic and specific serotonergic antidepressant
NSAIDs	non-steroid anti-inflammatory drug
PDQ	Perceived Deficits Questionaire
PMDA	Pharmaceutical and Medical Devices Agency

PT	Preferred Term
PTE	Pretreatment Event
PTP	press through package
QIDS	Quick Inventory of Depressive Symptomatology
SAE	serious adverse event
SDS	Sheehan Disability Scale
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	selective serotonin reuptake inhibitor
SUSARs	Suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TSH	thyroid-stimulating hormone
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Lu AA21004 (generic name: vortioxetine hydrobromide) is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and 5-HT transporter (5-HTT) inhibitor. This novel antidepressant with a different profile from existing medications has been under development in Japan and overseas. As of December 2014, Lu AA21004 has been approved for marketing as a drug for the treatment of MDD in countries including the U.S., Europe and Australia.

Depression is a mental disease mainly characterized by a depressed mood and a loss of interest or pleasure, and is additionally characterized by thought or concentration difficulties, an appetite decrease or increase, anxiety, a feeling of worthlessness or guilt, and thoughts related to suicide (suicidal ideation) as well as somatic symptoms including sleep disturbances and fatigability.[1][2] With advances of basic research and clinical studies, the etiology and pathology of depression have been gradually revealed, but not fully elucidated so far.

Depression is a common disease worldwide, with the estimated lifetime prevalence above 10%. The onset age is estimated to be from 20 to 50 years old in half of patients; however, the onset in children and the elderly has been also reported.[3] In the U.S., the prevalence of depression in aged 18 to 29 years is approximately 3-fold higher than that in more than 60 years, and, after early adolescence, the prevalence in women is 1.5 to 3-fold higher than in men, showing that the prevalence of depression varies widely depending on age and sex.[4]

The course of depression varies from only 1 episode in a lifetime to a lifelong disorder with recurrent episodes, and some patients suffer from long-term depressive symptoms despite treatments. Depression is therefore a significant mental and social burden and economic loss for not only patients but also their family, which treatment is necessary.[3]

The goal of treatment for depression is to improve patients' mental and social quality of life by effectively alleviating the depressive symptoms. Depression is mainly treated with pharmacotherapy and psychotherapy, and these treatments are selected according to the severity and pathological condition.[3] As pharmacotherapy in patients with moderate to severe depression, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) have been widely used. These antidepressants, however, have problems such as patients with inadequate response and adverse effects; therefore, development of an antidepressant with a novel profile can broaden treatment options and optimize treatment for depression.

4.1.1 Clinical Pharmacology

Results of clinical pharmacology studies in Japan and overseas are summarized below.

Lu AA21004 was slowly absorbed after oral administration, and the Tmax was approximately 7 to 11 hours. The absolute bioavailability of Lu AA21004 was approximately 75%. The

pharmacokinetics of Lu AA21004 was linear within the dose range between 2.5 and 60 mg. The plasma concentration of Lu AA21004 reached steady state after approximately 2-week multiple doses, and the accumulation index was 5 to 6 based on AUC following multiple doses of 5 to 20 mg/day. There was no food effect on the pharmacokinetics of Lu AA21004.

Lu AA21004 was extensively metabolized in the liver, primarily through oxidation or glucuronic acid conjugation, and CYP2D6 was shown to be the primary enzyme in metabolism of Lu AA21004 to the major metabolite Lu AA34443. Lu AA34443 was pharmacologically inactive, and the active metabolite Lu AA39835 did not cross the blood-brain barrier, although Lu AA39835 was slightly detected in plasma, suggesting that these metabolites are less likely to contribute to the pharmacological effect of Lu AA21004. In addition, Lu AA21004 and its metabolites did not induce or inhibit CYP isozymes *in vitro*, suggesting that clinical significant drug-drug interactions with Lu AA21004 are less likely to occur.

The T1/2 of Lu AA21004 was approximately 66 hours, and two- thirds of its metabolites were excreted in urine, and one-third were excreted in feces. The excretion of unchanged Lu AA21004 was slightly noted in feces.

After multiple doses of Lu AA21004, 5-HTT occupancy in raphe nuclei was approximately 50% at doses of 5 mg/day, 65% at 10 mg/day, and 80% or more at 20 mg/day.

Based on results of studies in Caucasian and Japanese subjects, there were no statistically significant differences in the pharmacokinetics and 5-HTT occupancy of Lu AA21004 between the races.

4.1.2 Overseas Phase II/III Clinical Studies

A total of 12 overseas placebo-controlled, double-blind, short-term studies (Studies 11492A, 11984A, 303, 304, 305, 13267A, 315, 316, 317, CCT-002, 12541A and 14122A) were conducted to evaluate the efficacy of Lu AA21004 for the treatment of MDD. Study CCT-002 was a multinational study including Japan.

The changes from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score were analyzed by mixed model repeated measures (MMRM) in the individual studies; and the results of the 11 of 12 studies mentioned above except for Study 12541A for elderly patients were used for meta-analysis. As for the mean changes from baseline in the MADRS total score at Week 6 or 8, the differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were -2.3 ($p = 0.007$), -3.6 ($p < 0.001$) and -4.6 ($p < 0.001$), respectively, and all of them were statistically significant. In addition, although the mean difference between the 15 mg group and placebo group was -2.6, not statistically significant. MADRS response rate (MADRS response is defined as a $\geq 50\%$ decrease from baseline in the MADRS total score) in the subjects treated with Lu AA21004 was 46% to 49%, whereas that in the subjects treated with placebo was 34% ($p < 0.01$). These results suggested Lu AA21004 at doses of 5 to 20 mg/day was effective.

For comprehensive safety evaluation including the above-mentioned short-term studies and long-term studies (Studies 11492C, 11984B, 301, 13267B and 314), treatment with Lu AA21004 at doses of 5 to 20 mg/day was safe and well tolerated. The most common TEAE in the

Lu AA21004 groups was nausea, and gastrointestinal TEAEs were occurred more frequently in female than male. Most TEAEs were mild or moderate and occurred within the first 2 weeks of treatment. In addition, TEAEs were usually transient, and did not generally lead to discontinuation of the study medication.

Abrupt discontinuation of antidepressants may result in discontinuation symptoms, however, there were no clinically relevant differences in the incidence or nature of discontinuation symptoms between the Lu AA21004 groups and placebo group.

The incidence of self-report sexual dysfunction in the Lu AA21004 groups was low, and was similar to that in the placebo group. In the study using a rating scale (Arizona Sexual Experience Scale) for sexual dysfunction, the incidence of sexual dysfunction at doses of 5 to 15 mg/day of Lu AA21004 was similar to that of placebo, but that at 20 mg/day was higher than placebo.

Lu AA21004 had no clinically significant effect on weight, heart rate, blood pressure, and hepatic and renal functions. Moreover, Lu AA21004 also had no clinically significant effect on ECG parameters (QT interval, QTc interval, PR interval and QRS interval). In a thorough QTc study in healthy adult subjects, Lu AA21004 at doses up to 40 mg/day had no potential for prolongation of QT/QTc intervals.

4.1.3 Japanese Phase II/III Clinical Studies

In Japan, 2 placebo-controlled, short-term studies (Study CCT-002 [multinational study] and Study CCT-003 [Japan local study]) were conducted in subjects with MDD. In addition, a long-term extension study (Study OCT-001) was conducted in those who completed Study CCT-003.

Study CCT-002 was conducted in 14 countries including Japan, Europe and the Asia Pacific region to evaluate the efficacy and safety of Lu AA21004 at doses of 5, 10 and 20 mg/day. For the mean changes from baseline in the MADRS total score at Week 8 (last observation carried forward [LOCF]) in the primary efficacy analysis (analysis of covariance [ANCOVA]), the mean differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were -0.61 ($p = 0.91$), -1.69 ($p = 0.30$) and -1.82 ($p = 0.24$), respectively. In addition, in the same analysis for Japanese population, the mean differences of the Lu AA21004 5, 10 and 20 mg group compared to the placebo group were 0.89, -2.74 and -3.45, respectively.

In Study CCT-002, Most TEAEs were mild or moderate, and TEAEs reported in more than 5% of subjects in any Lu AA21004 groups were nausea, nasopharyngitis, headache, dizziness, constipation, dry mouth, and insomnia. Of these, TEAEs with higher ($\geq$ 2-fold) incidence in any Lu AA21004 groups than that in placebo group were nausea, constipation, dry mouth, dizziness and insomnia.

In Study CCT-003, the efficacy and safety of Lu AA21004 at doses of 5 and 10 mg/day were evaluated in Japanese subjects with MDD. For the mean changes from baseline in the MADRS total score at Week 8 (LOCF) in the primary efficacy analysis (ANCOVA), the mean differences of the Lu AA21004 5 and 10 mg group compared to the placebo group were -2.03 ($p = 0.10$) and -1.04 ($p = 0.40$), respectively.

In Study CCT-003, TEAEs reported in more than 5% of subjects in any Lu AA21004 groups were nausea, diarrhoea, nasopharyngitis, somnolence, headache, and suicidal ideation. Of these, TEAEs with higher (≥2-fold) incidence in the Lu AA21004 groups than that in the placebo group were nausea and suicidal ideation. For suicidal ideation, the incidence in the 10 mg group (8 subjects; 6.6%) was higher than in the placebo group (2 subjects; 1.6%) and 5 mg group (1 subject; 0.8%). In general, most TEAEs were mild or moderate, suggesting that there were no significant safety concerns about Lu AA21004.

In the open-label long-term extension study (Study OCT-001), the safety of 52 week treatment of Lu AA21004 at flexible doses of 5 to 20 mg/day was evaluated in subjects who completed Study CCT-003. In Study OCT-001, TEAEs reported in more than 5% of subjects were nasopharyngitis, nausea, seasonal allergy, headache, weight increased, diarrhoea, vomiting, alanine aminotransferase (ALT) increased, somnolence, malaise, influenza, and blood creatine phosphokinase increased. No long-term specific TEAEs were observed, and most TEAEs were mild or moderate, suggesting that there were no significant safety concerns in a long-term treatment of Lu AA21004.

4.2 Rationale for the Proposed Study

In Europe and the U.S., the efficacy and safety of Lu AA21004 were demonstrated at doses of 5 to 20 mg/day and Lu AA21004 has already been approved for marketing. For 2 short-term studies (Studies CCT-002 and CCT-003) including Japanese MDD patients, there are no statistically significant differences in the efficacy between any Lu AA21004 groups and the placebo group; however, in Study CCT-002, changes from baseline in the MADRS total score in the 10 and 20 mg groups were grater than in the placebo group in both overall population and Japanese population, and these results appeared to be supported by the result of 10 mg group in Study CCT-003.

Based on these results, if a statistically significant difference between the Lu AA21004 10 or 20 mg group and the placebo group is shown in the planned study (Study CCT-004), it is considered that the hypothesis of the efficacy of Lu AA21004 at doses of 10 and 20 mg in the Japanese population in Study CCT-002 can be verified.

The results of Studies CCT-002, CCT-003 and OCT-001 suggested that there were no significant safety concerns about Lu AA21004 at the dose up to 20 mg, but further data collection may provide more appropriate safety evaluation.

From the above, this study is designed as an additional phase III study to evaluate the efficacy and safety of Lu AA21004 in Japanese patients with MDD.

Pharmacogenomic analyses may be conducted to evaluate a possible contribution of genetic polymorphism on drug response affecting the efficacy and safety of Lu AA21004. Participation of subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research with banked samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the efficacy of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.

5.1.2 Secondary Objectives

- To evaluate the safety and tolerability of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) after 8 weeks of treatment in Japanese patients with MDD.
- To evaluate the efficacy of Lu AA21004 (10 or 20 mg/day) on cognitive functions after 8 weeks of treatment in Japanese patients with MDD.

5.1.3 Additional Objectives

- To analyze the plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 using population pharmacokinetic analyses.

5.2 Endpoints

5.2.1 Efficacy Endpoints

5.2.1.1 Primary Endpoint

- Change from baseline (i.e. at the start of the double-blind treatment period) in the MADRS total score after 8 weeks of treatment.

5.2.1.2 Secondary Endpoints

- MADRS response after 8 weeks of treatment (LOCF).
  (MADRS response is defined as a ≥50% decrease in the MADRS total score from baseline).
- MADRS remission after 8 weeks of treatment (LOCF).
  (MADRS remission is defined as the MADRS total score of ≤10).
- Change from baseline in the Hamilton Depression Rating Scale (HAM-D17) total score after 8 weeks of treatment (LOCF).
- Clinical global impression scale-Improvement (CGI-I) score after 8 weeks of treatment (LOCF).
- Change from baseline in the clinical global impression scale-Severity (CGI-S) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Sheehan Disability Scale (SDS) score after 8 weeks of treatment (LOCF).

- Change from baseline in the Digit Symbol Substitution Test (DSST) score after 8 weeks of treatment (LOCF).
- Change from baseline in the Perceived Deficits Questionnaire (PDQ-5) score after 8 weeks of treatment (LOCF).

5.2.2 Pharmacokinetic Endpoint

- Plasma concentrations of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835.

5.2.3 Safety Endpoints

- Adverse events
- Weight
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

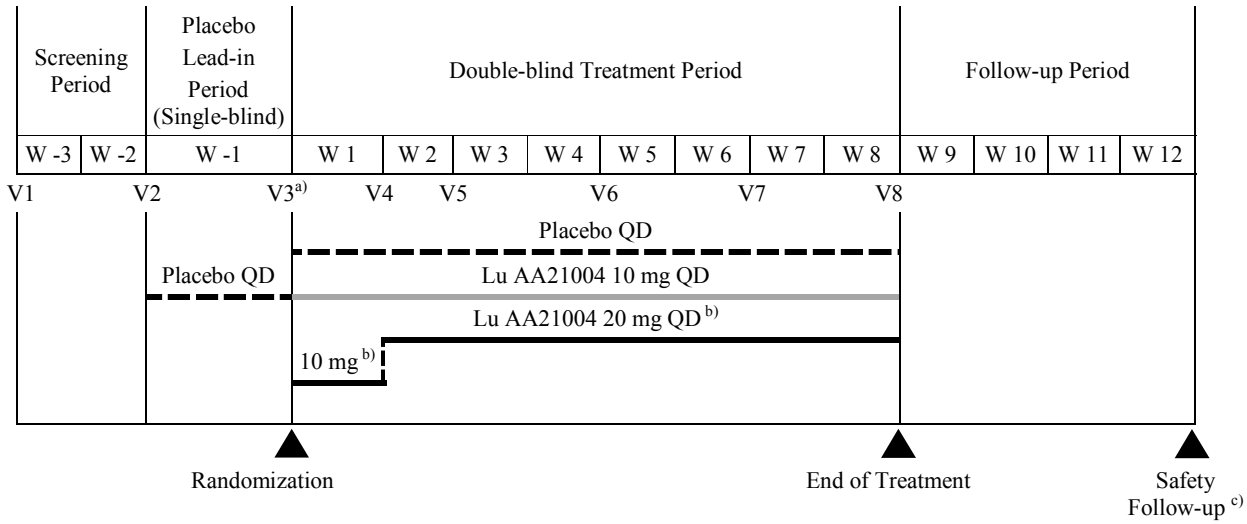
This is a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the efficacy and safety of 8-week treatment of 2 fixed doses of Lu AA21004 (10 or 20 mg/day) in Japanese subjects with MDD.

This study consists of a 2-week screening period, a 1-week single-blind placebo lead-in period, an 8-week double-blind treatment period and a 4-week safety follow-up period. Subjects who fulfill all inclusion criteria and none of exclusion criteria at the start of screening period (Visit 1) and at the start of placebo lead-in period (Visit 2) will move into the placebo lead-in period and receive placebo once daily for 1 week in a single-blind manner. Afterwards, these who fulfill all the inclusion criteria and none of the exclusion criteria at the start of double-blind treatment period (Visit 3) will move into the double-blind treatment period and will be randomized in a 1:1:1 ratio to one of the following treatment groups: the placebo group, the Lu AA21004 10 mg/day group or the Lu AA21004 20 mg/day group. Subjects in the placebo group and the Lu AA21004 10 mg/day group will receive placebo and Lu AA21004 10 mg, respectively, once daily from the day after Visit 3 for 8 weeks in a double-blind manner. Subjects in the Lu AA21004 20 mg/day group will receive Lu AA21004 10 mg once daily from the day after Visit 3 for 1 week and thereafter Lu AA21004 20 mg once daily for 7 weeks in a double-blind manner. Subjects in any treatment groups will visit study sites at Week 1, 2, 4, 6 and 8 during the double-blind treatment period for examinations/observations/assessments.

A safety follow-up contact (visit or phone call) will be made 4 weeks after the completion of the double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or the double-blind treatment period will be requested to visit the study site for the end-of study assessments within 7 days after the discontinuation decision is made wherever possible, and will be contacted 4 weeks after the last dose of the study medication for safety follow-up.

A schematic of the study design is shown in Figure 6.a.

A schedule of examinations/observations/assessments is listed in Appendix A.



W: week, V: visit, QD: once daily
a) Subjects will be randomized on the day of visit at the start of double-blind treatment period (Day -1). Subjects will start the double-blind treatment from the next day (Day 1).
b) Subjects will receive 10 mg/day for the first 1 week, and then increase the dose to 20 mg/day from the 2nd week.
c) Safety follow-up assessment will be conducted by visit to the site or on telephone.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Subject Population

It has been reported that the placebo response rate in subjects with single major depressive episode is higher than that in subjects with recurrent major depressive episode.[5] Since it is important to exclude subjects with high placebo response from clinical studies of antidepressants, subjects with recurrent major depressive episode are eligible for this study. In order to adequately evaluate the efficacy and safety, subjects with moderate to severe MDD are eligible for this study, and subjects with mental disorder other than MDD are excluded from this study.

6.2.2 Study Design

This study is designed based on Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of PFSB/ELD dated 16 November 2010).[3]

A double-blind, randomized, placebo-controlled study is designed for adequate evaluation of the drug efficacy and safety and is used as a standard study design for antidepressants. The use of placebo has continued to be a subject of discussion on the grounds of possible worsening of depressive symptoms or potential increase in suicidal risk; however, there is no evidence that assignment to placebo results in permanent harm or an increased risk of committing suicide.

Subjects at significant risk of suicide are ineligible for this study. Furthermore, suicidal risk of a subject will be assessed using C-SSRS at every visit.

The subjects will be informed about the possibility of receiving placebo, the possible risks with placebo, and their right to withdraw from the study at any time. To a subject who discontinues the study, any other appropriate treatment will be provided based on the investigator's decision.

In addition, a 1-week placebo lead-in period is set prior to the double-blind treatment period to exclude subjects who highly respond to placebo from the study, and thereby subjects who have significantly improvement or aggravation of depressive symptoms during the placebo lead-in period will be excluded.

Justification for sample size is described in Section 13.3.

6.2.3 Doses

In overseas phases II and III studies, the efficacy of Lu AA21004 at doses of 5, 10 and 20 mg/day was shown, with no significant safety concerns. In addition, based on the results of meta-analyses in 11 placebo-controlled, double-blind, short-term studies, the differences of the mean changes from baseline in the MADRS total score at Week 6 or 8 between the Lu AA21004 5, 10 or 20 mg group and the placebo group were -2.3 ($p = 0.007$), -3.6 ($p < 0.001$), and -4.6 ($p < 0.001$), respectively, showing that the difference with the placebo group became greater with the dose increase of Lu AA21004.

In Study CCT-002 for subjects with MDD including Japanese, Lu AA21004 was safe up to a dose of 20 mg/day. And although no statistically significant differences had been demonstrated in the efficacy between the Lu AA21004 groups and the placebo group, the efficacy of Lu AA21004 in the 10 and 20 mg groups was grater than in the placebo group in both overall population and Japanese population.

From the results of previous Japanese and overseas studies above, since there were no significant safety concerns about Lu AA21004 up to a dose of 20 mg/day and Lu AA21004 at doses of 10 and 20 mg/day is expected to be effective, these 2 doses will be assessed in this study.

6.2.4 Endpoints

MADRS or HAM-D is recommended for efficacy assessments in Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of PFSB/ELD dated 16 November 2010).[3] Based on the guideline, the MADRS, which is designed to be sensitive to the changes in severity of core symptom of depression, will be used for the primary endpoint evaluation [6], and the HAM-D for the secondary endpoint evaluation in this study.[7] CGI-S and CGI-I will be used to assess subject's overall severity and improvement of depression.[8] In addition to these objective assessments of symptoms, SDS will be used in this study to assess patient's subjective treatment effects on social function disabilities due to depression.[9]

Results of overseas studies of Lu AA21004 showed that Lu AA21004 improved cognitive functions in subjects with MDD. In this study, DSST and PDQ-5 will be used to explore the effect of Lu AA21004 on cognitive functions in Japanese subjects with MDD.

Safety and tolerability of Lu AA21004 will be evaluated by monitoring of AEs, vital signs, weight, clinical laboratory tests, ECGs, and physical examinations. In addition with these safety evaluations, since it is important to assess suicidal risk for clinical evaluation of antidepressants, suicidal risk will be assessed using C-SSRS at each visit in this study.[10][11]

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject suffer from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x).
4. The subject is a man or a woman aged 20 to 75 years (both inclusive) at the time of informed consent.
5. The reported duration of the current major depressive episode is 3 to 12 months (both inclusive) at the start of screening period.
6. The subject has a MADRS total score ≥26, a HAM-D17 total score ≥18, and a CGI-S score ≥4 at the start of screening period, the start of placebo lead-in period and the start of double-blind treatment period.
7. A female subject of childbearing potential* who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent to the end of the follow-up period.

* Definitions of a female subject of childbearing potential are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities of pregnancy are defined in Section 9.1.14 Pregnancy.

<Justification for Inclusion Criteria>

Criteria 1 and 2 were set as standard requirements to conduct clinical studies.

Criterion 3 was set to identify the target disease and diagnostic criteria for this study. In addition, in order to reduce the possibility of enrolling subjects who highly respond to placebo, the primary diagnosis was set as recurrent MDD.

Criterion 4 was set for the lower limit of age as 20 years old because it was the adult age under the Civil Code. In addition, since the previous pivotal phase II or III studies set 75 years old as the upper limit of age, the upper limit of age in this study was set as 75 years old in the light of the possible comparison with the previous data.

Criterion 5 was set to enroll subjects who had persistent major depressive episode for at least 3 months in consideration of diagnostic certainty. The upper limit of episode duration was set as 12

months since, in general, subjects with chronic depressive symptoms are highly likely to have other concurrent mental disorder and the low possibility that the depressive symptoms would completely disappear with antidepressant drugs.

Criterion 6 was set to enroll subjects with moderate or more severe MDD in severity as eligible for this study.

Criterion 7 was set with respect to the safety risk related to pregnancy in female subjects.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has any following current or past history of psychiatric disorder and/or neurological disorder:
   - Any current psychiatric disorder other than MDD as defined by DSM-IV-TR (To be assessed by Mini International Neuropsychiatric Interview: MINI). A subject who exhibits symptoms of anxiety is eligible unless the subject fulfills the diagnostic criteria for a current anxiety disorder per DSM-IV-TR.
   - Current diagnosis or history of manic, mixed or hypomanic episode, MDD with psychotic features, schizophrenia or any other psychotic disorder (including substance-related mental disorders, or mental disorders due to a general medical condition) as defined by DSM-IV-TR.
   - Current diagnosis or history of any substance-related disorder (except nicotine and caffeine-related disorders) as defined by DSM-IV-TR.
   - The subject with a positive urine drug screening result at the start of screening period or the start of placebo lead-in period. In case that a subject showed positive test result at the start of screening period because the test was conducted before washout of pretreatment drug, the subject is eligible as long as he/she shows negative result at the start of placebo lead-in period.
   - Presence or history of any clinically significant neurological disorder (including epilepsy).
   - Any neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).
   - Any DSM-IV-TR axis II disorder.
2. The subject has the current or previous major depressive episode which were considered by the investigator to have been resistant to 2 or more adequate antidepressants treatments of at least 6 weeks duration each at sufficient doses.
3. The subject has received any augmentation therapy (e.g. lithium, T3/T4, lamotrigine, sodium valproate, carbamazepine, additional atypical antipsychotic, or concomitant use of other antidepressant, etc.) for the current major depressive episode.

4. In the opinion of the investigator, the subject has experienced significant number of major depressive episodes in the past, and is suspected of disease other than MDD.
5. In the opinion of the investigator, the subject has experienced the first major depressive episode at his/her young age, and is suspected of disease other than MDD.
6. The subject has a MADRS total score at the start of double-blind treatment period that has improved or aggravated by 25% or more from the score at the start of placebo lead-in period.
7. The subject is significantly non-compliant with the study medication in the placebo lead-in period; e.g., not taking the study medication for 6 or more consecutive days.
8. The subject has received electroconvulsive therapy, vagus nerve stimulation, or repetitive transcranial magnetic stimulation therapy within 6 months prior to the screening period, or plans to initiate such therapy during the study.
9. The subject is receiving cognitive-behavioral therapy or psychotherapy at the time of informed consent, or plans to initiate such therapy during the study.
10. The subject is at significant risk of suicide or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS at the start of screening period, the start of placebo lead-in period or the start of double-blind treatment period, or has attempted suicide within 6 months prior to the start of screening period.
11. The subject has experienced any environmental change (e.g. temporary retirement, returnment, change of residence) considered by the investigator to have the potential to impact on the efficacy evaluation, or plans such environmental changes during the study.
12. The subject is currently receiving drug therapy for thyroid dysfunction.
13. The subject is currently receiving hormonal therapy for gynecological disease.
14. The subject has taken excluded medications during the protocol-specified period, or will require to take excluded medications during the study.
15. The subject has previously received vortioxetine.
16. The subject has received study medication in a previous clinical study of Lu AA21004 (including this study).
17. The subject has a clinically significant chronic liver disease.
18. The subject has a history of severe allergy or hypersensitivity to drugs.
19. The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, neoplastic, skin and subcutaneous tissue disorders, eye disorders, or metabolic disturbance.
20. The subject has clinically significant abnormal vital signs as determined by the investigator at the start of screening period, placebo lead-in period, or double-blind treatment period.

21. The subject has clinically significant abnormal ECG as determined by the investigator, at the start of the screening period, placebo lead-in period, or double-blind treatment period.
22. The subject has clinically significant abnormal findings of clinical laboratory tests as determined by the investigator, or has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN at the start of screening period or placebo lead-in period.
23. If female, the subject is pregnant or lactating.
24. The subject has a disease or takes medications that could, in the opinion of the investigator, interfere with the evaluation of the safety, tolerability, or efficacy.
25. The subject is, in the opinion of the investigator, unsuitable for this study for any other reason.

<Justification for Exclusion Criteria>

Criteria 1, 4, and 5 were set to exclude subjects or the possible subjects with concurrent mental or neurological disorder other than MDD and to adequately evaluate the efficacy and safety for the target disease.

Criterion 2 was set to exclude subjects or the possible subjects with refractory major depression and include adequate subjects for the evaluation of drug effect.

Criterion 3 was set to exclude subjects who have received augmentation therapy and include adequate subjects for the evaluation of drug effect since subjects who are required to receive augmentation therapy may have refractory major depression or concurrent mental or neurological disorder other than MDD.

Criterion 6 was set to exclude subjects who highly respond to placebo and include adequate subjects for the evaluation of drug effect. Subjects who abruptly worsen their symptoms in a short time are also excluded from the study in consideration of the appropriateness of drug effect evaluation and the safety of subjects.

Criterion 7 was set because it influences the evaluation in the placebo lead-in period.

Criteria 8, 9, 11 to 13 were set because they could influence the evaluation of efficacy.

Criteria 10, 17 to 22 were set with respect to the safety of subjects.

Criteria 14 and 24 were set because they could influence the evaluation of efficacy and safety.

Criterion 15 was set because the bias toward Lu AA21004 based on their treatment experience could influence the evaluation of the efficacy and safety.

Criterion 16 was set to avoid duplicated evaluation of subjects.

Criterion 23 was set with respect to the safety risk for pregnant women, fetuses, neonates, or nursing infant.

Criterion 25 was set to exclude subjects who are considered to be unsuitable for this study for any other reason.

7.3 Excluded Medications and Treatments

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Any treatments for depression other than the study medication, including electroconvulsive therapy, vagus nerve stimulation, repetitive transcranial magnetic stimulation, cognitive-behavioral therapy or psychotherapy are prohibited during the study.

A list of prohibited/restricted concomitant medication is provided in Table 7.a.

Table 7.a List of Prohibited or Restricted Concomitant Medications

Drug Class	Comments or Exceptions
84 days before the start of double-blind treatment period (Day -84) through the end of double-blind treatment period (Visit 8) or early termination	
(1) Any investigational drug	
Start of the screening period (Visit 1) through the end of double-blind treatment period (Visit 8) or early termination	
(2) Antidepressants	Including MAOIs.
(3) Anxiolytics (tranquilizers)	Including benzodiazepines.
(4) Hypnotics	Non-benzodiazepines (zolpidem, zopiclone, and eszopiclone) are allowed. However, use of these drugs should be kept to the minimum necessary, and use for 2 consecutive days and use at the night before a study visit are NOT allowed. In addition, the type and dose of non-benzodiazepines should NOT be changed from the start of placebo lead-in period (Visit 2) to the end of double-blind treatment period (Visit 8) or early termination.
(5) Antipsychotics	Depot antipsychotics are prohibited within 6 months prior to the start of double-blind treatment period.
(6) Mood stabilizers	Including lithium, valproate, valpromide.
(7) Psychoactive herbal remedies/supplements	Including St. Johns Wort, kava kava, valerian, ginkgo biloba.
(8) Psychotropic agents not otherwise specified	Including tryptophan, melatonin, and dopamine agonists.
(9) Analeptics	
(10) Anti-ADHD	
(11) Anti-Alzheimer's disease	
(12) Anticonvulsants	
(13) Anti-Parkinson's disease	
(14) Erectile dysfunction drugs	
(15) Anorexics	
(16) Antimigraines	
(17) Antiemetics/antinauseants	Including dopamine antagonists. Only phosphoric acid preparations, bismuth and cola syrup are allowed.
(18) Interferon	
(19) Systemic steroids	Oral preparation and injection are NOT allowed.

(20) Antibiotics	Rifampicin (oral preparation and injection) is NOT allowed.
Start of the placebo lead-in period (Visit 2) through the end of double-blind treatment period (Visit 8) or early termination	
(21) Antiarrhythmics of class Ia, Ic	
(22) Antiulcer drugs	Omeprazole, cimetidine, and sulpiride are NOT allowed.
(23) Anticoagulants/antiplatelet treatment	Including low dose of aspirin as antiplatelet treatment. Low-molecular weight heparins are allowed as needed.
(24) Antidiarrheal agents	Loperamide, bismuth, and kaolin preparations are allowed.
(25) Antihistamines	Loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine are allowed.
(26) Antineoplastics	
(27) Hormones	Chronic use for contraception or treatment of benign prostatic hyperplasia are allowed.
(28) Hypoglycemic agents	Chronic use is allowed.
(29) Insulin	Chronic use is allowed without major change of dose or administration.
(30) Calcium antagonist	Chronic use is allowed without major change of dose or administration.
(31) Narcotic analgesics	Topical administration including for dental use is allowed.
(32) NSAIDs	Episodic use is allowed. Selective COX-2 inhibitors, acetaminophen, and topical NSAIDs are allowed.
(33) Cough/cold agents	Episodic use is allowed. However, chronic use of preparations containing ephedrine, pseudoephedrine, and codeine are NOT allowed for more than 1-week treatment.

MAOI = monoamine oxidase inhibitor, ADHD = attention deficit hyperactivity disorder,
NSAIDs = nonsteroidal anti-inflammatory drugs, COX-2 = cyclooxygenase-2

<Justification for Prohibited or Restricted Concomitant Medications>

(1) was set since other investigational drug could influence the evaluation of the efficacy and safety.

(2) was set since antidepressants could influence the evaluation of the efficacy. Especially, concomitant use of monoamine oxidase inhibitors (MAOIs) was prohibited because concomitant use of MAOIs could enhance serotonin action and influence the evaluation of the efficacy, and because the safety of subjects should be ensured.

(3) was set since anxiolytics (tranquilizers) could improve anxiety which was known to an accompanying symptom of depression and influence the evaluation of the efficacy.

(4) was set since hypnotics could improve insomnia which was known to an accompanying symptom of depression and influence the evaluation of the efficacy. Concomitant use of non-benzodiazepines was allowed as needed because the extent of anxiolytic and carry-over effects of non-benzodiazepines was relatively weak, and thus these effects had only a small influence on efficacy evaluation.

(5) to (13) were set since these drugs had psychotropic activity or central nervous effects and

could influence the evaluation of the efficacy.

(14) was set since erectile dysfunction drugs could improve sexual dysfunction and could influence the evaluation of the efficacy and safety.

(15) was set since anorexics influence the appetite assessment related to depression.

(16) and (17) were set since antimigraines and antiemetics/antinauseants could act on serotonin receptors and influence the evaluation of the efficacy and safety. Especially, concomitant use of antiemetics/antinauseants was prohibited because adverse events associated with the study medication should be appropriately evaluated.

(18) and (19) were set since interferon and systemic steroids could induce depressive symptoms and influence the evaluation of the efficacy.

(20) was set since antibiotics could decrease the plasma drug concentration by inducing drug metabolic enzymes and influence the evaluation of the efficacy and safety.

(21) and (22) were set since antiarrhythmics of class Ia, Ic, and antiulcer drugs could increase the plasma drug concentration by inhibiting drug metabolic enzymes and influence the evaluation of the efficacy and safety

(23) was set since concomitant use of anticoagulants/antiplatelet treatment drugs could enhance bleeding tendency.

(24) was set since gastrointestinal adverse events associated with the study medication should be appropriately evaluated.

(25) was set since drowsiness, an adverse drug reaction of antihistamines, could attenuate insomnia, which was known to an accompanying symptom of depression and influence the evaluation of the efficacy. Concomitant use of only loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine, which are considered to cause less drowsiness, was allowed.

(26) was set since antineoplastics could influence the evaluation of the efficacy and safety.

(27) and (28) were set since hormones and hypoglycemic agents could influence the evaluation of the efficacy and safety. However, chronic use of these drugs at a certain dose was allowed as having little influence on the evaluation.

(29) and (30) were set since insulin and calcium antagonists could induce depressive symptoms. However, chronic use of insulin or calcium antagonist at a certain dose was allowed as having little influence on the efficacy evaluation.

(31) was set since analgesic action of narcotic analgesics could influence the evaluation of the efficacy. However, topical administration such as for dental use is allowed since narcotic analgesics have only a small influence on the evaluation.

(32) was set since the concomitant use of NSAIDs could cause upper gastrointestinal bleeding. However, the episodic use of NSAIDs as well as the concomitant use of selective COX-2 inhibitors, acetaminophen, and topical NSAIDs was allowed since these treatments had a

relatively lower effect on gastrointestinal adverse events.

(33) was set since some cough/cold agents increase the serotonin concentration of the central nervous system. Concomitant use of ephedrine and codeine for more than 1 week was not allowed due to their addictiveness.

7.4 Diet, Fluid, and Activity Control

The investigator or study collaborator should instruct subjects on the following items:

1. The subject must be punctual for visit, undergo physical examination and predefined examinations. If the subject cannot visit, he/she should inform the investigator or study collaborator as soon as possible.
2. If the subject experiences a worsening of conditions on any day the site visit is not scheduled, he/she should inform the investigator or study collaborator of the worsening by telephone or other manners as soon as possible and seek instructions.
3. The subject must take the study medication as instructed by the investigator. If the subject is noncompliant with study treatment, he/she should inform the investigator or study collaborator of the noncompliance with treatment at visit. The subject must return unused study medication and study medication sheets at visit.
4. The subject must not take any medications including over-the-counter products other than medications as instructed by the investigator without advance consulting (except for emergency).
5. If the subject consults other medical institution from the time of informed consent to the end of the follow-up period, notify the physician of medical institution of the subject's participation in this study.
6. If the subject consults other medical institution from the time of informed consent to the end of the follow-up period, notify the investigator of the circumstances and therapy.
7. The subject must visit the site under fasted conditions at Visits 3 and 8 or Early Termination Visit. For visits serum chemistry test is scheduled, the subject visits the site under fasted conditions wherever possible.
8. Female subject of childbearing potential who is sexually active with a nonsterilized male partner must routinely use adequate contraception from the time of informed consent to the end of the follow-up period.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the case report form (eCRF) using the following categories. For the subject who prematurely discontinues the study before entry into the placebo lead-in period or randomization, refer to Section 9.1.18 or 9.1.20, respectively.

1. **Pretreatment event (PTE) or adverse event (AE)**
   The subject has experienced a pretreatment event (PTE) or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. **Liver function test (LFT) abnormalities**
   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study medication treatment:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
   - ALT or AST >5 × ULN and persists for more than 2 weeks, or
   - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. **Significant protocol deviation**
   The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. **Lost to follow-up**
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. **Voluntary withdrawal**
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. (i.e., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category.)
6. **Study termination**
   The sponsor, IRB, or regulatory agency terminates the study.
7. **Pregnancy**
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.

8. **Lack of efficacy**
   The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
9. **Medication noncompliance**
   The subject did not take the study medication for 6 or more consecutive days.
10. **Other**
    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5.1 Additional Guidance for Withdrawal Criteria

Any signs of suicidal risk will be assessed throughout the study by C-SSRS and MADRS assessments and clinical judgment of the investigator. If the subject has a significant risk of suicide in the opinion of the investigator, or the subject has the MADRS score of ≥5 on item 10 (suicidal thoughts), the subject will prematurely discontinue the study.

If subject's underlying diseases become exacerbated, and the investigator concludes any excluded medications or treatment is required, the subject will prematurely discontinue the study.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

Table 8.a Study Medication

Name	Active Substance	Dosage Form	Strength	Manufacture
Lu AA21004 tablet	1-[2-(2,4-dimethyl-phenyl sulfanyl)-phenyl]-piperazine, hydrobromide	Indistinguishable round biconvex tablets	10 mg or 20 mg	Takeda Pharmaceutical Company Limited
Placebo tablet	None		–	

The study medications are identical in appearance.

As for the study medications for the placebo lead-in period, 14 tablets of placebo are packaged in 1 press-through pack (PTP) sheet, and a single sheet is enclosed in an outer carton. The 1 outer carton (including 7 days' spare tablets) will be provided to each subject in the placebo lead-in period.

As for the study medications for the double-blind treatment period, 14 tablets of Lu AA21004 or placebo are packaged in 1 PTP sheet. For Week 1 in the double-blind treatment period, 1 sheet (including 7 days' spare tablets) is enclosed in an Inner Carton 1, and, for Weeks 2 to 8 in the double-blind treatment period, 5 sheets (including 21 days' spare tablets) are enclosed in an Inner Carton 2. Inner Cartons 1 and 2 are packed together in an outer carton. The 1 outer carton will be provided to each subject in the double-blind treatment period.

The outer carton is labeled with a note that the formulation therein is used for a clinical study and pertinent information of the name and quantity of the study medication, the sponsor's name and address, manufacturing number, and storage conditions.

8.1.2 Storage

The study medications should be stored at room temperature (1°C to 30°C).

The study medication must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. The study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

For the placebo lead-in period, administration of the study medication will be started on the day after Visit 2, and subjects will orally take 1 tablet of placebo once daily.

For the double-blind treatment period, administration of the study medication will be started on the day after Visit 3, and subjects will orally take 1 tablet of Lu AA21004 at a dose of 10 mg or 20 mg or placebo once daily.

The investigator or designee should instruct subjects to take the study medication at the same time, a certain time in the morning to the extent possible, throughout the study. The study medication can be taken under both fed and fasted conditions.

At each visit, subjects will be provided with necessary and sufficient amount of the study medications to be used by next visit by the investigator or designee. The investigator or designee must instruct subjects to bring the all remaining study medication and container (PTP sheets) at each visit.

The dose (tablet count) that will be provided to each group and regimen are shown in Table 8.b.

Table 8.b Dose and Regimen

Treatment Group	Regimen	Tablet Count/Dose		
		Placebo Lead-in Period	Double-blind Treatment Period (Week 1)	Double-blind Treatment Period (Weeks 2 to 8)
Placebo Group	Oral, once daily	Placebo tablet ×1	Placebo tablet ×1	Placebo tablet ×1
Lu AA21004 10 mg/day Group	Oral, once daily	Placebo tablet ×1	Lu AA21004 10 mg tablet ×1	Lu AA21004 10 mg tablet × 1
Lu AA21004 20 mg/day Group	Oral, once daily	Placebo tablet ×1	Lu AA21004 10 mg tablet ×1	Lu AA21004 20 mg tablet ×1

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of the study medication to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. This includes any concomitant medication received at a dose greater than that prescribed to the subject.

All cases of overdose will be documented as AEs on an AE page of the eCRF according to Section 10.2.1, and should be reported as a special interest AE according to Section 10.2.1.3 (with or without associated AEs). Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure in Section 10.2.2.

In the event of an overdose of the study medication, the investigator should take general symptomatic and supportive treatment, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration,

pulse, blood pressure, and other appropriate signs should be monitored and general supportive treatment should be conducted.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive the next available medication ID number allocated to each study site. The Medication ID Number will be entered onto the eCRF.

8.3 Randomization Code Creation and Storage

Randomization personnel (a person designated by the sponsor) will generate the randomization code. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The emergency key code administration center will maintain the emergency key code until its breaking for an emergency or completion of database lock of all subjects.

Since analytical results of the plasma concentration may jeopardize maintenance of study blinding, the analytical laboratory will keep the final analytical results and not disclose to a third party until unblinding of the study. The analytical laboratory will report the results to the sponsor after they receive the notification of unblinding of the study. However, the analytical laboratory may disclose the results to the sponsor through a responsible person for randomization before unblinding of the study taking measures to secure the blinding such as reassignment of the medication number so that persons in the laboratory may not identify a subject. The detailed procedure will be specified in the separately created manual for handling of biological specimen for pharmacokinetic analysis.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject.

For unblinding, the investigator may contact the emergency key code administration center and obtain allocation information of the study medication.

The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking, and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

For details of unblinding procedure, refer to the manual for Breaking of Emergency Key Code.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage, and management of study drug created by the sponsor, according to which the site designee will appropriately manage the

sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

A separate informed consent form pertaining to pharmacogenomic research must be obtained prior to collecting a sample for Pharmacogenomic Research for this study (see Section 9.1.16). The provision of consent to research in pharmacogenomics is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, alcohol use, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any mental disorders other than MDD (including dysthymic disorder, generalized anxiety disorder, obsessive-compulsive disorder, as defined by DSM-IV-TR) that resolved within 1 year prior to signing of informed consent. Medical history of MDD (past major depressive episode) to be obtained will include determining whether the subject had MDD according to Section 9.1.4.2.

Medication history information to be obtained includes any medication that stopped prior to signing of informed consent and used for treatment of the current major depressive episode or accompanying symptoms. Name of medication used, dose level, unit, dose frequency, route of administration, and the dates of the initial dose and the last dose must be recorded.

9.1.3 Diagnosis of MDD

Diagnosis of MDD and other psychiatric disorders must be based on DSM-IV-TR criteria. In addition, the Mini International Neuropsychiatric Interview (MINI) must be used as an auxiliary diagnostic tool. MINI is a structured diagnostic interview designed to provide a brief standardized evaluation of major Axis I psychiatric disorders in DSM-IV-TR. The investigator can use the MINI after a training session for diagnosis of MDD. Only the version provided by the sponsor that has been validated in Japanese will be used in this study.

9.1.4 Assessments of Major Depressive Episode

9.1.4.1 Current Major Depressive Episode

The following items will be assessed for the current major depressive episode.

- Start date
- Symptom (Select from 9 symptoms listed below as defined by DSM-IV-TR.)
- Psychotherapy (yes or no)

<Symptoms of Major Depressive Episode>

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of weight in a month), or decrease or increase in appetite nearly every day.

(4) Insomnia or hypersomnia nearly every day.

(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

(6) Fatigue or loss of energy nearly every day.

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

9.1.4.2 Past Major Depressive Episode

The following items will be assessed for past major depressive episode.

- Start date and duration of each past major depressive episode.
- Antidepressant drug treatment for each past major depressive episode (yes or no). If the subject has received an antidepressant drug, category of the drug (select from SSRIs, SNRIs, or other antidepressant drugs.) and duration will be recorded.

9.1.5 Physical Examination Procedure

A physical examination will consist of the following body systems:

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

All subsequent physical examinations after administration of the study medication in the double-blind treatment period should assess clinically significant changes from the examinations at the start of double-blind treatment period (Visit 3).

9.1.6 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height will be collected in centimeters without decimal places, and weight will be collected in kilograms (kg) to 1 decimal place. The BMI will be calculated by the sponsor to 1 decimal place with the formula provided below:

$$\text{Metric: BMI} = \text{weight (kg)}/\text{height (m)}^2$$

9.1.7 Vital Sign Procedure

Vital signs will include body temperature (infra-axillary measurement), sitting blood pressure (resting more than 5 minutes), and pulse (bpm).

9.1.8 Efficacy Evaluation

The efficacy will be evaluated using rating scales (MADRS, HAM-D, CGI-S/I, SDS, DSST, and PDQ-5). These assessments should be performed by the investigator who has sufficient experience in clinical practice of diagnosing and treating MDD and who was approved by the sponsor as a rater in this study. The same rater should, whenever possible, assess the same subject throughout the study.

In principle, the MADRS should be performed first at visits that the above-mentioned multiple rating scales will be performed. Efficacy data using these rating scales should be recorded in eCRF by the next visit of the subject at the latest.

In addition, self-report of depressive symptoms by subjects will be performed using Quick Inventory of Depressive Symptomatology (QIDS-J). For QIDS-J, any sequencing order with other rating scales is allowed. QIDS-J data will not be recorded in the eCRF.

9.1.8.1 Rating and Rating Training for MDD

Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS will be used for a primary efficacy measurement. The MADRS is a depression rating scale consisting of 10 items representing the core symptoms of depression.[6] The MADRS is rated using Structured Interview Guide for MADRS (SIGMA). The rating should be based on a clinical interview with the subject, moving from broadly phrased questions about

symptoms to more detailed questions. The rating is performed based on the most severe condition of the subject during the past 1 week, and each item is rated from 0 to 6. Items 2 to 10 are based on subject report, and Item 1 is based on the observation of the subjects. The rater must decide whether the rating for each item lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). Each item score and the total score of all items should be recorded on the eCRF.

Before the first rating, the investigators (hereinafter referred to as [potential] raters in this section) will attend a MADRS training session. Potential raters will watch and score a recorded MADRS interview (video/DVD). A discussion will follow the training session to achieve alignment among raters on the scoring of each individual item.

The sponsor will qualify the raters who achieve the scoring in the training session, and issue a certificate. No subject may be rated before the rater receives the certificate. For potential raters who cannot attend the training session or who are not qualified in the training session, similar MADRS training will be held in each study sites.

If a rater is changed or added during the course of the study, the newly appointed rater must complete all training requirements satisfactorily and must be approved by the sponsor.

Hamilton Depression Rating Scale (HAM-D)

The HAM-D is a depression rating scale that assesses overall symptoms of depression including somatic symptoms. The rater must rate each item score between 0 to 2/3/4 based on a clinical interview with the subject.[7] The rating should be based on patient's condition during the past 1 week prior to the time of assessment. The HAM-D21 is used for rating, and total score of the first 17 items is used as HAM-D17 total score. Each item score and the HAM-D17 total score should be recorded on the eCRF. Prior to the first rating, potential raters will attend a session on concerns to be addressed for the rating of HAM-D.

Clinical Global Impression Scale (CGI)

The CGI consists of 2 sub-scales: CGI-S and CGI-I.[8] The CGI-S assesses the physician's impression of the subject's current mental disorder state. The rater should use his/her total clinical experience with this subject population and rate the current severity of the subject's mental disorder on a 7-point scale. The CGI-I assesses the subject's improvement (or worsening). The rater is required to assess the subject's condition relative to baseline* on a 7-point scale. In all cases, the assessment should be made independent of whether the rater believes the improvement is study medication-related or not. Each score of CGI-S and CGI-I should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the rating of CGI.

* The start day of the double-blind treatment period (Visit 3) is defined as baseline. However, for the assessment at the start of double-blind treatment period (Visit 3) or early termination visit prior to the start of double-blind treatment period, CGI should be assessed comparing with the score at the start of placebo lead-in period (Visit 2).

9.1.8.2 Social Function Assessment

Sheehan Disability Scale (SDS)

The SDS is a scale that assesses disabilities in 3 social function domains subjectively.[9] The subject self-rates the extent to which his or her work/school, social life/leisure activities, and home life/family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale. The SDS also addresses the number of days the above functions were lost or under-productive due to the symptoms. Each item score should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the rating of SDS.

9.1.8.3 Cognitive Function Assessments

Digit Symbol Substitution Test (DSST)

The DSST is a test battery used for assessment of cognitive functions. In the DSST, subjects are shown 9 digit-symbol pairs and required to pair the same digit and symbol combination. Levels of cognitive functions are assessed by the number of correct symbols (0 to 133 scores) within the time limit. DSST scores should be recorded on the eCRF. At a start of the placebo lead-in period (Visit 2), subjects will complete the sample items prior to the actual test, but the results of the sample items should not be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of DSST.

Perceived Deficits Questionnaire (PDQ-5)

The PDQ-5 is a self-report questionnaire by subjects used for assessment of their cognitive functions. PDQ-5 consists of 5 questions and provides an assessment of several domains of cognitive functions: attention, retrospective memory, prospective memory, and planning and organization. Sub-scores of each item score (0 to 4 scores) and the total score of all items should be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of PDQ-5.

9.1.8.4 Self-report Assessment of Depressive Symptoms and Assessment Monitoring

Quick Inventory of Depressive Symptomatology (QIDS-J)

The QIDS-J is a basic self-report depression scale, and the partially revised version provided by the sponsor will be used for this study. Subjects will enter the responses to each questions of the QIDS-J into the terminal. The rater should not see the responses and not record them on the eCRF. The responses will be reviewed by the expert who has adequate experience in assessment of depression. Appropriateness of the efficacy evaluation will be monitored by comparing with results of other efficacy evaluation of the relevant subject.

9.1.9 Suicidal Risk Assessments

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical study. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.[10][11] Responses to each question will be recorded on the eCRF. Prior to the first rating, potential raters will attend a rating session on concerns to be addressed for the assessment of C-SSRS.

9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through Visit 8 or Early Termination Visit), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF.

9.1.11 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent, except for accompanying symptoms of MDD. This includes clinically significant laboratory, vital sign, ECG, or physical examination abnormalities noted at the first examination after signing of informed consent in the opinion of the investigator. The condition (i.e., diagnosis) should be described.

9.1.12 Procedures for Clinical Laboratory Samples

The items of clinical laboratory tests are shown in Table 9.a. Samples will be collected and handled in accordance with the separate operation manual. For clinical laboratory tests, the maximum volume of blood at any single visit is approximately 10 mL.

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**	
Red blood cells (RBC)	Albumin	Glucose (fasting or non-fasting) [a)]
White blood cells (WBC)	AST	Total protein
Hemoglobin	ALT	Potassium
Hematocrit	γ-GTP	Sodium
Platelets	Alkaline phosphatase	Calcium
Neutrophils	Total bilirubin	Chloride
Eosinophils	Direct bilirubin	Lipids (fasting or non-fasting) [a)]
Basophils	(Conjugated bilirubin)	Triglycerides
Lymphocytes	Creatinine	Total Cholesterol
Monocytes	Creatine kinase	High-density lipoprotein cholesterol
	Blood urea nitrogen (BUN)	Low-density lipoprotein cholesterol (direct measurement)
	Uric acid	
Hormonal Test	**Urinalysis**	
Thyroid stimulating hormone (TSH)	Protein (qualitative)	Urine pH
Free T_4 [b)]	Glucose (qualitative)	Microscopic examination [c)] (white blood cells, red blood cells, and casts)
	Occult blood (qualitative)	
Pregnancy test (female subjects of childbearing potential only)		
Urine human chorionic gonadotropin (hCG)		
Urine Drug Screening [d)]		
Amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaines, morphines, phencyclidines, and tricyclic antidepressants		

a) Blood will be collected under fasted conditions at Visits 3 and 8 or Early Termination Visit. For other visits, blood will be collected under fasted conditions wherever possible.
b) When TSH value is outside the normal range, free T_4 will be measured. If a clinically significant abnormality of thyroid gland is found based on the results of TSH and free T_4, the subject will be excluded from the study.
c) Microscopic examination will be performed if abnormality is found in any item in urinalysis.
d) If the subject has a positive urine drug result, he/she will be excluded from the study. However, when the subject has a positive urine test result at Visit 1 because the urine test was performed prior to washout of pretreatment drug, the subject is eligible for the study if he/she has a negative drug test result at Visit 2.

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and hormonal test. The local laboratory will perform the pregnancy test and urine drug screening. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-GTP, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. If the ALT or AST remains elevated >3 × ULN on these 2 consecutive occasions, the abnormality should be recorded as a special interest AE (hepatic impairment) by the investigator, and follow

the procedure specified in Sections 10.1.5.2 and 10.2.1.3. After additional examinations and detailed monitoring, the investigator must contact the sponsor for consideration of possible discontinuation of the study medication, discussion of the relevant subject details and possible alternative etiologies.

If subjects experience ALT or AST >3 × ULN and total bilirubin >2 × ULN, the investigator must refer to instructions in Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject and Section 10.2.3 Reporting of Abnormal Liver Function Tests.

9.1.13 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, to the end of the follow-up period, female subjects of childbearing potential (e.g., non-sterilized or premenopausal female subjects) who are sexually active with a nonsterilized male partner must use adequate contraception. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed, and subjects will receive continued guidance with respect to the avoiding pregnancy as part of the study procedures (Appendix A).

At visits when pregnancy tests are performed, subjects must be confirmed of having a negative urine hCG pregnancy test, as well as at the follow-up examination.

9.1.14 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any study medication should be immediately discontinued.

If the pregnancy occurs during administration of active study medication from the start of the study medication in the double-blind treatment period to the end of the follow-up period, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the attachment.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician (obstetrics and gynecology specialist) that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.15 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: RR interval, PR interval, QT interval, QRS interval, and QTcB interval. QTcF interval will be calculated by the sponsor. ECG traces recorded on thermal paper should be photocopied to avoid degradation of trace over time.

9.1.16 Pharmacogenomic Sample Collection

One 5-mL whole blood sample for pharmacogenomics will be collected at the start of placebo lead-in period (Visit 2) or at the earliest possible time during the study from subjects who signed informed consent of pharmacogenomics and entered into the placebo lead-in period for possible exploratory investigation of markers enabling the prediction of drug response.

Pharmacogenomic sample should not be collected from any subject who has received comparable bone marrow transplant or whole blood transfusion within 6 months of any sample collection.

See the separately created procedure for collecting, handling, and storage of pharmacogenomic samples.

9.1.17 Pharmacokinetic Sample Collection and Analysis

9.1.17.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples will be collected in concurrence with blood collection for clinical laboratory tests. The exact date and time of the blood collection and dosing times of the last 2 doses prior to the blood collection will be recorded on the eCRF. Refer to the separately created procedure for collection, handling, and shipping of blood samples.

Since drug concentrations of subjects in the placebo group will not be measured, the assignment personnel will send an operation manual to the central laboratory to identify samples of subjects in the placebo group. Drug concentration data will be reported to the sponsor after unblinding of the study.

9.1.17.2 Bioanalytical Methods

Plasma concentrations of Lu AA21004 and its metabolites (Lu AA34443 and Lu AA39835) will be analyzed with the validated LC/MS/MS method.

9.1.18 Documentation of Screen Failure Prior to Entrance into Placebo Lead-in Period

For all subjects who signed informed consent and prematurely discontinue the study prior to entry into the placebo lead-in period, the investigator should complete the eCRF. The registration center should be contacted as a notification of screen failure prior to entry into the placebo lead-in period.

The primary reason for screen failure prior to entry into the placebo lead-in period will be recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria <specify the reason.>
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify the reason.>
- Study termination
- Other <specify the reason.>

The identification numbers assigned to subjects who prematurely discontinues prior to entry into the placebo lead-in period should not be reused.

9.1.19 Documentation of Study Entrance into Placebo Lead-in Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria at the start of placebo lead-in period are eligible for entrance into the placebo lead-in period.

If the subject is found to be not eligible for the placebo lead-in period, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.20 Documentation of Screen Failure Prior to Randomization

For all subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization, the investigator should complete the eCRF. The registration center should be contacted as a notification of discontinuation after entry into the placebo lead-in period and prior to randomization.

The primary reason for screen failure after entry into the placebo lead-in period and prior to randomization is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria <specify the reason.>
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify the reason.>
- Study termination
- Other <specify the reason.>

The end-of-study evaluation will be performed for all subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization according to Section 9.3.5.

9.1.21 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization and entrance into the double-blind treatment period.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for screen failure on the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring unused study medication containers (PTP sheets)/unused medications to each dispensing site visit. The dates of the initial and last dosing, as well as any details where a subject takes more or less of the study medications than the specified dose, will be recorded on the eCRF.

If a subject is significantly noncompliant with the study medication (e.g., 6 or more consecutive doses missed), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Period

Informed consent must be obtained prior to the initiation of any study procedures.

The examinations/observations/assessments listed below will be performed at the start of screening period (Days -22 ± 10; Visit 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting a subject who prematurely discontinues the study prior to entry into the placebo lead-in period.

- Demographics, medical history, and medication history
- Diagnosis of MDD
- Assessments of the major depressive episode
- Physical examination
- Weight and height
- Vital signs

- Concomitant medications
- Concurrent medical conditions
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Urine drug screening
- ECG procedure
- C-SSRS
- PTE assessment
- MADRS
- HAM-D
- CGI-S

9.3.2 Placebo Lead-in Period

The examinations/observations/assessments listed below will be performed at the start of placebo lead-in period (Day -8 ± 3; Visit 2). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects assessed to be eligible will enter the placebo lead-in period. See Section 9.1.18 for procedures for documenting subjects who prematurely discontinue the study prior to entry into the placebo lead-in period.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Urine drug screening.
- Blood sampling for pharmacogenomics* (subjects who provided written consent only)
- ECG procedure
- C-SSRS
- PTE assessment
- MADRS
- HAM-D

- CGI-S
- SDS
- DSST
- PDQ-5
- QIDS-J
- Dispense of the study medication (for the placebo lead-in treatment)

* Blood sampling for pharmacogenomics will be performed at the start of placebo lead-in period (Visit 2) or at the earliest possible time during the study.

9.3.3 Start of Double-blind Treatment Period/Randomization

The examinations/observations/assessments listed below will be performed at the start of double-blind treatment period (Day -1; Visit 3). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects assessed to be eligible will be randomized according to Section 8.2 and enter the double-blind treatment period. See Section 9.1.20 for documenting subjects who prematurely discontinue the study after entry into the placebo lead-in period and prior to randomization.

The examinations/observations/assessments at Visit 3 should be regarded as baseline evaluations.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- HAM-D
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 2).
- SDS
- DSST

- PDQ-5
- QIDS-J
- Randomization
- Dispense of the study medication (for the double-blind treatment [Inner Carton 1])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

9.3.4 Double-blind Treatment Period

Visit 4

The examinations/observations/assessments listed below will be performed at 1 week after the start of double-blind treatment period (Day 7 ± 1; Visit 4).

- Vital signs
- Concomitant medications
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- DSST
- PDQ-5
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 5

The examinations/observations/assessments listed below will be performed at 2 weeks after the start of double-blind treatment period (Day 14 ± 3; Visit 5).

- Vital signs
- Concomitant medications
- C-SSRS
- PTE/AE assessment

- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 6

The examinations/observations/assessments listed below will be performed at 4 weeks after the start of double-blind treatment period (Day 28 ± 3; Visit 6).

- Weight
- Vital signs
- Concomitant medications.
- Clinical laboratory tests
- Pregnancy test (female subjects of childbearing potential only)
- Pharmacokinetic sampling
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

Visit 7

The examinations/observations/assessments listed below will be performed at 6 weeks after the start of double-blind treatment period (Day 42 ± 3; Visit 7).

- Vital signs

- Concomitant medications
- C-SSRS
- PTE/AE assessment
- MADRS
- CGI-S
- CGI-I (assessed comparing with a CGI score at Visit 3).
- QIDS-J
- Dispense of the study medication (for the double-blind treatment [Inner Carton 2])
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

9.3.5 End of Double-blind Treatment Period or Early Termination

The examinations/observations/assessments listed below will be performed at 8 weeks after the start of double-blind treatment period (Day 56 ± 3; Visit 8) as evaluation at the end of double-blind treatment period. Subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period will be requested to visit the study site for early termination examinations/observations/assessments within 7 days after the day of study discontinuation wherever possible.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Clinical laboratory tests (fasted)
- Pregnancy test (female subjects of childbearing potential only)
- Pharmacokinetic sampling (not performed at early termination)
- ECG procedure
- C-SSRS
- PTE/AE assessment
- MADRS
- HAM-D
- CGI-S
- CGI-I*

- SDS
- DSST
- PDQ-5
- QIDS-J
- Collection of the study medication dispensed at the last visit/Consultation about subjects' compliance

* The CGI-I score will be assessed comparing with that at Visit 3. However, at early termination prior to Visit 3, the CGI-I score will be assessed by comparing with that at Visit 2.

For all randomized subjects, the investigator must complete the End of Study eCRF page.

After evaluation at the end of double-blind treatment period or early termination, standard therapy may be performed as needed.

9.3.6 Follow-up Period

A safety follow-up assessment will be conducted at 12 weeks after the start of double-blind treatment period (Day 84 ± 5). For subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period, the follow-up assessments will be made 28 ± 5 days after the last dose of the study medication. The follow-up assessments may either be conducted as a visit to the site or as a telephone contact. In the follow-up, the following will be assessed: outcomes of AEs continuing at Visit 8 or early termination visit, new SAEs developing during the follow-up period, and special interest AEs will be assessed. Female subjects of child-bearing potential will be asked to confirm whether they are pregnant or not.

9.3.7 Post Study Care

The study medication will not be available upon completion of the subject’s participation in the study.

9.4 Biological Sample Retention and Destruction

Samples of 5-mL whole blood collected for pharmacogenomics will be stored frozen at the pharmacogenomic specimen storage facility (see the contact listed in the attachment 1; hereinafter referred to as specimen storage facility).

The collected samples will be retained for 20 years from the day when a first pharmacogenomic sample was collected during the study.

When subjects request disposal of a stored sample during the retention period, the site will ask the specimen storage facility to destroy the sample via the sponsor according to the procedure. The specimen storage facility will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents (including medical records) have been destroyed which could identify the subject, and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when pharmacogenomic investigation has been conducted, the remaining sample will be destroyed and the results of pharmacogenomic investigation of the anonymized subject will be retained by the sponsor.

The sponsor will build a management system required for protection of the subject's personal information, define standards for collecting, storage, and destruction of samples, and prepare appropriate procedures.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Of pre-existing conditions (present at the time of signing of informed consent), events that are considered accompanying symptoms of MDD should NOT be recorded as concurrent medical conditions, PTEs, or AEs.
- Other pre-existing conditions are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences an abnormality (e.g., internal bleeding due to blood sampling) associated with the baseline evaluations, the abnormality should be recorded as a PTE and recorded on eCRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). The investigator should ensure that the event term recorded captures the change in the condition (e.g., "worsening of hypertension").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, the investigator should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, the investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. The investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. The investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedures is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures (e.g., cosmetic surgery) performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- All cases of overdose with any medication, including the case without manifested side effects, are considered AEs and will be recorded on the AE page of the eCRF. In addition, cases of overdose will be reported as special interest AEs.

Suicidality events:

- A completed suicide is always captured as an SAE based on its fatal outcome. Furthermore, active suicidal behavior such as suicidal ideation with a specific plan and suicide attempt will also be collected as an SAE.
- Unless the event in question meets the definition of "serious," suicidal thoughts or suicidal ideation without a specific plan or action will be collected as a non-serious AE in accordance with the standard AE reporting requirements.
- A subject who presents with self-mutilation should be asked by the investigator to clarify whether the subject was attempting suicide. If the subject was attempting suicide, the behavior will be collected as an SAE, and the specific suicidal behavior (e.g., wrist cutting) will be recorded in the eCRF. If the subject was not attempting suicide, the behavior will be collected as a non-serious AE in accordance with the standard AE reporting requirements.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.*
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

* The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including seizure and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial lung disease)
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death
	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxin shock

The following events are also to be considered SAEs.

- Completed suicide
- Active suicidal ideation
- Active suicidal behavior such as suicide attempt
- Self-injury with suicide attempt

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) is 1 of scientific and medical concern specific to the compound or program. In this study, skin reaction, allergic reaction, hepatic impairment, and overdose are defined as special interest AEs. Ongoing monitoring and communication by the investigator to Takeda may be appropriate, and if the events occur, they will be reported according to Section 10.2.1.3. Such events may require further investigation in order to characterize and understand them.

10.1.5.1 Skin and Allergic Reaction

When the causal relationship between rash or allergic reaction and the study medication is assessed as probable or possible, rash or allergic reaction will be reported as a special interest AE according to Section 10.2.1.3 after the nature and the site are characterized. When the causal relationship between rash or allergic reaction and the study medication is assessed as not related, rash or allergic reaction is not required to be reported as a special interest AE.

When rash or allergic reaction develops, the subject should be adequately examined for any clinical features that may suggest the development of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome (SJS). In addition, the subject should be monitored for the appearance of any of the following signs:

a) Involvement of mucous membrane or the conjunctiva

b) Development of skin pain

c) Urticaria, blistering, or other types of skin lesions

d) Angioedema

If a subject presents with symptoms of a systemic reaction (e.g., generalized rash), or signs of severe rash, or if it is clinically necessary, the following laboratory parameters should also be investigated and monitored accordingly: complete blood count with differentials, liver and renal function tests, and urinalysis. If deemed necessary by the investigator, subjects should be received examination by a dermatologist, and photographs of the skin rash and/or skin biopsies will be obtained as needed.

10.1.5.2 Hepatic Impairment

If a subject has ALT or AST >3 × ULN, and follow-up laboratory tests (see Section 9.1.12) also shows ALT or AST >3 × ULN, it should be reported as a special interest AE according to Section 10.2.1.3. In addition, the relevant subject details and possible alternative etiologies other than the study medication should be investigated.

If the abnormality falls under a drug-induced liver function abnormality that may lead to severe hepatic impairment (see Section 10.2.3), it should also be reported as an SAE.

10.1.5.3 Overdose

For overdose, refer to Section 8.1.4. All cases of overdose will be documented as AEs on an AE page of the eCRF and should be reported as special interest AEs according to Section 10.2.1.3 (with or without associated adverse events).

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Probable:	An AE that has a strong temporal relationship to the study medication(s), or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
Possible:	An AE that has a suggestive temporal relationship to the study medication(s), and an alternative etiology is equally or less likely.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of the study medication(s) or that can reasonably be explained by other factors, such as underlying diseases, concurrent medical conditions, concomitant drugs and concurrent treatments (that is, there is no causal relationship between the study medication and the AE).

An AE is considered causally related to the use of the study medication when the causality assessment is *probable* or *possible*.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of AEs/PTEs will be determined based on the criteria described below.

AE/PTE	Start Date
Signs, symptoms, and diseases (diagnosis)	Date when the subject or the investigator first notices the sign or symptom of the AE
Asymptomatic disease	Date when a definite diagnosis is determined based on the results of diagnostic testing. Even if obsolete findings are indicated based on the test findings or the approximate time of onset can be estimated, the date when a definite diagnosis is made should be recorded.
Worsening of concurrent medical conditions or PTEs	Date when the subject or the investigator first notices worsening of the disease or symptom.
Normal in the initial assessment after signing of informed consent but abnormal in the subsequent assessment (for PTEs) Abnormal in the assessment after the start of the study medication (for AEs)	Date when the test is performed in which a clinically significant abnormal test value is observed
Abnormal in the initial assessment after signing of informed consent and has worsened in the subsequent assessment (for PTEs) Abnormal in the assessment at the start of the study medication and has worsened in the subsequent assessment (for AEs)	Date when the test is performed in which a medically significant elevation, reduction, increase or decrease in clinical laboratory test values is observed

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The AE/PTE not determined to have resolved at the end of the study is assessed as ongoing

10.1.11 Frequency

Episodic AEs/PTEs (e.g., constipation, diarrhea, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Medication

The action taken for the study medication is classified and defined as follows:

Drug withdrawn	The study medication is stopped due to the particular AE (including withdrawal at the subject's discretion).
Dose not changed	The dose is not changed even after the occurrence of the particular AE. This shall apply in case the study medication is stopped due to another AE. This shall also apply, for example, in case the study medication is stopped for any reason other than intervention for the particular AE, such as the subject's negligence.

Unknown	For example, attempts to contact the subject are unsuccessful and the course of the particular AE after the start date cannot be followed.
Not Applicable	For example, the study medication has already been completed or stopped before the onset of the particular AE.

10.1.13 Outcome

The outcome of AEs/PTEs is classified as follows:

Category	Assessment Criteria
Recovered/Resolved	• The symptom or finding has disappeared or resolved. • The abnormal laboratory value has improved to the normal range or to the level at baseline (for AEs) or at the first assessment after signing of informed consent (for PTEs).
Recovering/Resolving	• The intensity is lowered by at least 1 grade. • The symptom or finding has almost disappeared. • The abnormal laboratory value has improved, but not to the normal range or the level at baseline (for AEs) or at the first assessment after signing of informed consent (for PTEs). • The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (no need to record the date of death).
Not recovered/not resolved	• There is no change in the symptom, finding, or laboratory value. • The intensity of the symptom, finding, or laboratory value on the last day of the observed period has got worsen than when it started. • An irreversible congenital anomaly. • The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" AE/PTE (no need to record the date of death).
Resolved with sequelae	• The subject recovered from an acute AE/PTE but was left with impairment that interferes with the subject's daily life.
Fatal	• There is a direct relationship between the death and the AE/PTE. • The direct relationship indicates that the AE/PTE caused or apparently contributed to the death. • The outcome of another AE/PTE reported in the same subject that is not determined (considered or estimated) as the cause of the death is not assessed as "fatal." • If the outcome is "fatal," the date of death should be recorded.
Unknown	• The course of the AE/PTE after the start date cannot be followed up as specified in the protocol due to hospital change or residence change.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication in the

placebo lead-in period. For subjects who discontinue prior to the first study medication administration in the placebo lead-in period, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication in the placebo lead-in period. Routine collection of AEs will continue until Visit 8 or Early Termination Visit.

Collection of SAEs or special interest AEs will continue until the end of the follow-up period.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the change (for permanent or irreversible PTEs). Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the change (for permanent or irreversible AEs). All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date
3. Frequency
4. Severity
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (probable, possible, not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs)
8. Outcome of event
9. Seriousness
10. Classification as special interest AEs (Yes or No)

C-SSRS will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. If it is determined that an AE not previously reported has been identified through this follow-up, normal reporting requirements should be applied.

AEs and serious PTEs will be followed up until resolution or until the investigator judges that further follow-up is not necessary.

10.2.1.3 Special Interest AE Reporting

If the special interest AE (refer to Section 10.1.5) occurs through the AE collection period, it should be reported to Safety Information Emergency Call Center, in principle (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The investigator should complete the Rash and Allergic Reaction, Hepatic Impairment or Overdose Form within 10 business days and report to Safety Information Emergency Call Center, in principle. In addition, the investigator should submit to the sponsor the original Rash and Allergic Reaction, Hepatic Impairment or Overdose Form.

The special interest AEs have to be recorded as AEs in the eCRF.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure. PTEs that fulfill the serious criteria described in Section 10.1.4 are also to be considered SAEs and should be reported in the same manner.

The investigator should report the SAEs with information required in the SAE form to Safety Information Emergency Call Center, in principle, within 1 business day of the first onset or subject's notification of the event. The investigator should prepare the completed SAE form within 10 calendar days and submit to Safety Information Emergency Call Center, in principle. In addition, the investigator should submit to the sponsor the original SAE form.

For the report within 1 business day, the information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be also reported to the sponsor if considered related to study participation. Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the investigator must contact the sponsor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests must also be performed (see Section 9.1.12). If the investigator considers that such liver function abnormality cannot be explained by any factor other than the study medication, the event should be reported as a SAE (see Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the detailed report becomes available at a later date, the investigator should complete a follow-up SAE form copy or provide other written documentation and report it immediately to the sponsor or Safety Information Emergency Call Center. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and the head of the study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee (CRO), SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of the study medication or that would be sufficient to consider changes in the administration of study medication or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff (the investigator, subinvestigators, and other study collaborators) in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The investigator must review the eCRFs for completeness and accuracy and must sign the appropriate eCRFs. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs.

- Laboratory test values measured at the central laboratory
- Observed drug concentrations

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail,

and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS), and safety analysis set.

The FAS, which will be used as a primary analysis set for efficacy analysis, is defined as "all subjects who were randomized and received at least 1 dose of the study medication in the double-blind treatment period."

The exact definition of each analysis set is specified in the Data Handling Rules for Statistical Analysis.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Data Handling Rules for Statistical Analysis must be finalized prior to unblinding.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Major background and demographic characteristics will be summarized overall and by treatment group.

13.1.3 Efficacy Analysis

Primary Efficacy Analysis for Primary Endpoint

The primary endpoint for this study is the change from baseline (i.e. at the start of double-blind treatment period) in the MADRS total score after 8 weeks of treatment.

Comparisons between each Lu AA21004 treatment group and the placebo group at Week 8 of the double-blind treatment period will be performed using the FAS based on MMRM analysis of covariance with the change from baseline in the MADRS total score as a dependent variable, and visit, treatment group, visit-by-treatment group interaction and baseline MADRS total score-by-visit interaction as fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom. Holm's step down method will be used to adjust the multiplicity for the comparisons. More specifically, let H_{01}, H_{02} be a family of hypotheses as follows:

H_{01}: $\mu_{Placebo} = \mu_{10\ mg}$
H_{02}: $\mu_{Placebo} = \mu_{20\ mg}$

Then let P_1 and P_2 denote the unadjusted p-values of tests for H_{01} and H_{02}, respectively. Order the p-values from the smallest to the largest, $P^{(1)}$, $P^{(2)}$ and let the corresponding null hypotheses be $H^{(1)}$, $H^{(2)}$. Holm's step-down method proceeds as follows:

Step 1: if $P^{(1)} > 0.025$, retain both null hypotheses $H^{(1)}$ and $H^{(2)}$, and stop. If $P^{(1)} \leq 0.025$, reject null hypothesis $H^{(1)}$ and go to Step 2.

Step 2: if $P^{(2)} > 0.05$, retain null hypothesis $H^{(2)}$. If $P^{(2)} \leq 0.05$, reject null hypothesis $H^{(2)}$.

Secondary Efficacy Analyses for Primary Endpoint

To check the robustness of the results, the same analysis as used for the primary efficacy analysis will be performed using the PPS.

For the FAS, an analysis of covariance (ANCOVA) model with the change from baseline in the MADRS total score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) as a dependent variable, treatment group as a fixed effect and the baseline MADRS total score as a covariate will be applied for comparisons between the placebo group and each Lu AA21004 treatment group.

Analyses for Secondary Endpoints

MADRS response (MADRS response is defined as a ≥50% decrease from baseline in the MADRS total score) and MADRS remission (MADRS remission is defined as the MADRS total score ≤10) after 8 weeks of treatment (LOCF) will be compared between treatment groups using logistic regression analysis including the baseline MADRS total score and treatment groups in the model.

The change from baseline in the HAM-D17 total score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline HAM-D17 total score as a covariate.

The CGI-I score after 8 weeks of treatment (LOCF) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline CGI-S score as a covariate.

The change from baseline in the CGI-S score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline CGI-S score as a covariate.

The change from baseline in the SDS score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline SDS score as a covariate.

The change from baseline in the DSST score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline DSST score as a covariate.

The change from baseline in the PDQ-5 score after 8 weeks of treatment (values at Week 8 [LOCF] − baseline) will be analyzed using an ANCOVA model with treatment groups as a fixed effect and the baseline PDQ-5 score as a covariate.

Two-sided tests with significance level at 5% will be used for all statistical tests. Ninety-five percent confidence intervals will be presented along with the P-values.

13.1.4 Pharmacokinetic Analysis

The population pharmacokinetic analysis of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 will be performed using the nonlinear mixed effect model (NONMEM). Pharmacokinetic parameters of individual subjects (e.g., AUC[0-tau], Cavg, Cmax) will be estimated and their correlation with relevant pharmacodynamic parameters (efficacy and tolerability/safety) will be explored. The population pharmacokinetic analysis plan will be prepared separately.

13.1.5 Safety Analysis

AEs

The definition of treatment-emergent adverse events (TEAE) will be described in the statistical analysis plan (SAP). TEAEs will be summarized using the safety analysis set. TEAEs will be coded using the MedDRA and will be summarized by system organ class (SOC) and preferred term (PT). No statistical testing or inferential statistics will be generated.

A subject who has developed a same TEAE more than once will be counted as 1 subject in the severity category corresponding to the maximum severity of the event.

Clinical Laboratory Test, Weight, Vital Signs, and ECG

Summary statistics of observed values and changes at each time point (values at each time point in the double-blind treatment period − baseline) will be calculated for clinical laboratory tests, vital signs, ECG parameters, and weight for each treatment group. Incidences of values that are outside normal ranges and are potentially and clinically significant will be calculated.

C-SSRS

Descriptive statistics of C-SSRS will be calculated at each time point for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A number of subjects planned to be enrolled in this study is 480 (160 per group). Assuming the true mean differences of 3.5 for the change from baseline in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between each Lu AA21004 group and the placebo group by 2-sample t-test. In addition, assuming the true mean differences of 3.0 for the change from baseline

in the MADRS total score between each Lu AA21004 group and the placebo group, this sample size will provide greater than 80% power to detect the difference between either the Lu AA21004 10 mg or 20 mg group and the placebo group. These power calculations assume a common standard deviation of 9.5 for the change from baseline in the MADRS total score, with a 2-sided level of 0.025.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, and informed consent documentation. It is important that the investigator, the subinvestigator, and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or signing of informed consent). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug no protocol activities, including the informed consent procedure may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

Regarding pharmacogenomic investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for pharmacogenomics investigations, and a research protocol will require prior approval of the company IRB in Japan.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by the IRB prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent form must be signed and/or sealed, and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign and/or seal using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and/or seal, and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed and/or sealed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. A copy of the signed and/or sealed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

The informed consent form for pharmacogenomic research in the clinical study of Lu AA21004 will be used to explain the pharmacogenomic research to subjects after explanation of the informed consent for the entry into the study. Pharmacogenomic samples will be collected from subjects who have consented to both the study and the pharmacogenomic research.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites (JAPIC-CTI) before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (JAPIC-CTI), as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Nakane Y, Arima K. Cause and Symptom of Depression. The Journal of Practical Pharmacy. 2000;51(2):826-34.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Translated by Takahashi S, Ono Y, Someya T. Igaku-Shoin. 2004.

[3] Guideline for Clinical Evaluation of Antidepressants (Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division; Notification No.1116-1 dated November 16 in 2010) (in Japanese).

[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Translated by Takahashi S, Ono Y, Someya T, Kanba S, Ozaki N, Mimura M, Murai T.. Igaku-Shoin. 2014.

[5] Bialik RJ, Ravindran AV, Bakish D, Lapierre YD., 1995. A Comparison of Placebo Responders and Nonresponders in Subgroups of Depressive Disorder. J Psychiatry Neurosci. 1995;20:265-70.

[6] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

[7] Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278-96.

[8] Guy W. ECDEU Assessment Manual for Psychopharmacology (Revised). Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health, Psychopharmacology Research Branch; 1976. p.193-198

[9] Olfson M, Fireman B, Weissman MM, Leon AC, Sheehan DV, Kathol RG, et al. Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry. 1997;154:1734-40.

[10] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. Am J Psychiatry. 2007;164(7):1035-43.

[11] Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the Assessment of Suicidality in Youth. CNS Spectr. 2007;12(2):156-62.

Appendix A Schedule of Study Procedures

	Screening Period	Placebo Lead-in Period [a]	Double-blind Treatment Period						Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET [c]**	**Follow-up [d]**
Week [b]	-3	-1	0	1	2	4	6	8/ET [c]	12 [d]
Day [b]	-22	-8	-1	7	14	28	42	56/ET [c]	84 [d]
Visit Window (Days) [b]	±10	±3	0	±1	±3	±3	±3	±3/-	±5
Informed consent	X [e]								
Inclusion/exclusion criteria	X	X [f]	X [f]						
Demographics, medical history, medication history	X								
Diagnosis of MDD	X								
Assessments of major depressive episode	X								
Physical examination	X	X	X					X	
Weight, height [g]	X	X	X			X		X	
Vital signs	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	
Concurrent medical conditions	X								
Clinical laboratory tests [h]	X	X	X			X		X	
Pregnancy test [i]	X	X	X			X		X	(-)
Urine drug screening	X	X							
Pharmacokinetic sampling						X		(X)	
Pharmacogenomic sampling [j]		(X)							
ECG	X	X	X			X		X	
C-SSRS	X	X	X	X	X	X	X	X	
PTE/AE assessment [k]	X	X	X	X	X	X	X	X	(-)
<Assessments with Rating Scales>									
MADRS	X	X	X	X	X	X	X	X	
HAM-D	X	X	X					X	
CGI-S	X	X	X	X	X	X	X	X	
CGI-I [l]			X	X	X	X	X	X	
SDS		X	X					X	
DSST		X [m]	X	X				X	
PDQ-5		X	X	X				X	
QIDS-J		X	X	X	X	X	X	X	
<Clinical Supply>									
Randomization			X						
Dispense study medication [n]		X	X	X	X	X	X		
Drug return/accountability/compliance			X	X	X	X	X	X	

ET = early termination

(a) In the placebo lead-in period, subjects will receive the study medication in a single-blind manner.
(b) The visit day in the double-blind treatment period is defined as Week 0 (Day -1). The day after Day -1 is defined as Day 1. All visit windows are in reference to the date of scheduled visit.
(c) Subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period will be requested to visit the study site for the end-of study examinations within 7 days after the day of study discontinuation, wherever possible, and will be assessed in the same way as at Visit 8 (except for blood sampling for pharmacokinetics).
(d) Safety follow-up assessments will be conducted. For subjects who prematurely discontinue the study during the placebo lead-in period or double-blind treatment period, the follow-up assessments will be made 28 ± 5 days after the last dose of the study medication. The follow-up assessments can either be conducted as a visit to the site or as a telephone contact. In the follow-up, the following will be assessed: outcomes of AEs continuing at Visit 8 (or the end-of study assessments if administration of the study medication is discontinued), new SAEs developed during the follow-up period, and special interest AEs. Female subjects of child-bearing potential will be asked to confirm whether they are pregnant or not.
(e) Informed consent must be obtained prior to the initiation of any study procedure including washout of excluded medications. Informed consent may be obtained prior to the visit window of Visit 1.
(f) Update at Visits 2 and 3.
(g) Height is measured at only Visit 1.
(h) Clinical laboratory tests will be performed under fasted conditions at Visits 3 and 8 or Early Termination Visit, and at other visits wherever possible.
(i) For women of child-bearing potential.
(j) Only for subjects who consent to provide pharmacogenomic samples, separately from consent of participation in the study. Pharmacogenomic samples for analyses will be collected at Visit 2 or thereafter, as soon as possible, during the study.
(k) PTEs will be collected prior to study medication administration in the placebo lead-in period, and AEs will be collected after study medication administration.
(l) The CGI-I score will be assessed by comparison with that at Visit 3. However, at Visit 3 or early termination prior to Visit 3, the score will be assessed by comparison with that at Visit 2.
(m) Subjects will complete the sample items prior to the actual test.
(n) At Visit 2, subjects will be dispensed the study medication for the placebo lead-in period. At Visit 3, subjects will be dispensed the study medication for the double-blind treatment period, Inner Carton 1, and Inner Carton 2 at Visits 4 to 7, with a necessary and sufficient amount of the study medication by next visit.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety, and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications, and responsibilities of individual personnel to the investigator and the study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing, and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of an SAE, immediately notify the director of the site and the sponsor in writing.
11. Determine the need of emergency key code blinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
14. Discuss any proposal from the sponsor including update of the protocol.
15. Notify the director of the site of the end of the study in writing.